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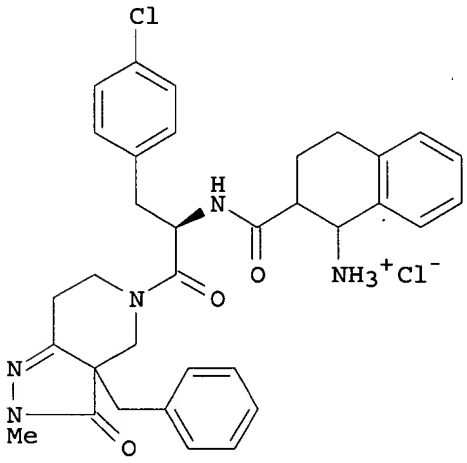
L15 ANSWER 1 OF 5 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 136:15253 CA
TITLE: **Melanocortin** receptor agonists, and preparation thereof, for therapeutic use
INVENTOR(S): Bakshi, Raman Kumar; Nargund, Ravi P.; Ye, Zhixiong
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001091752	A1	20011206	WO 2001-US17014	20010525
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002004512	A1	20020110	US 2001-867309	20010529

PRIORITY APPLN. INFO.: US 2000-207918 P 20000530
OTHER SOURCE(S): MARPAT 136:15253
GI



I

AB The invention discloses compds. and derivs. thereof which are agonists of the human **melanocortin** receptor(s) and, in particular, are selective agonists of the human **melanocortin**-4 receptor (**MC-4R**). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the activation of **MC-4R**, e.g. obesity, diabetes, **sexual dysfunction**, including erectile dysfunction and female **sexual dysfunction**. Prepn. of e.g. I is described.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Melanocortin** receptor agonists, and preparation thereof, for therapeutic use

AB The invention discloses compds. and derivs. thereof which are agonists of the human **melanocortin** receptor(s) and, in particular, are selective agonists of the human **melanocortin**-4 receptor (**MC-4R**). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the activation of **MC-4R**, e.g. obesity, diabetes, **sexual dysfunction**, including erectile dysfunction and female **sexual dysfunction**. Prepn. of e.g. I is described.

ST **melanocortin** 4 receptor agonist prepn therapeutic; obesity diabetes treatment **melanocortin** receptor agonist; **sexual dysfunction** treatment **melanocortin** receptor agonist; erectile dysfunction treatment **melanocortin** receptor agonist

IT Drug delivery systems
(capsules; **melanocortin** receptor agonist prepn. for therapeutic use)

IT Anticholesteremic agents
(cholesterol sequestrants; **melanocortin** receptor agonist prepn. for therapeutic use, and use with other agents)

IT Sexual behavior
(disorder; **melanocortin** receptor agonist prepn. for therapeutic use)

IT Sequestering agents
(for cholesterol; **melanocortin** receptor agonist prepn. for therapeutic use, and use with other agents)

IT Sexual behavior
(impotence; **melanocortin** receptor agonist prepn. for therapeutic use)

IT Pituitary hormone receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**melanocortin** 4; **melanocortin** receptor agonist prepn. for therapeutic use)

IT Antidiabetic agents
Antiobesity agents
Drug delivery systems
(**melanocortin** receptor agonist prepn. for therapeutic use)

IT Dopamine agonists
(**melanocortin** receptor agonist prepn. for therapeutic use, and use with other agents)

IT Sulfonylureas
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**melanocortin** receptor agonist prepn. for therapeutic use, and use with other agents)

IT Pituitary hormone receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**melanocortin**; **melanocortin** receptor agonist prepn.

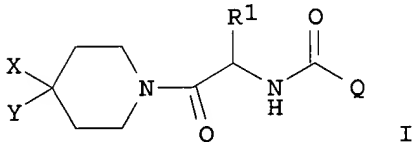
for therapeutic use)
IT Adrenoceptor antagonists
(.alpha.2-; **melanocortin** receptor agonist prepn. for therapeutic use, and use with other agents)
IT Adrenoceptor agonists
(.beta.3-; **melanocortin** receptor agonist prepn. for therapeutic use, and use with other agents)
IT 82785-45-3, Neuropeptide Y
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists; **melanocortin** receptor agonist prepn. for therapeutic use, and use with other agents)
IT 9001-42-7, .alpha.-Glucosidase 9028-35-7, HMG-CoA reductase 9068-52-4, Phosphodiesterase V
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; **melanocortin** receptor agonist prepn. for therapeutic use, and use with other agents)
IT 378741-82-3P 379266-73-6DP, isomers 379266-73-6P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**melanocortin** receptor agonist prepn. for therapeutic use)
IT 378741-76-5 379266-96-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**melanocortin** receptor agonist prepn. for therapeutic use)
IT 59433-90-8P 378741-77-6P 378741-78-7P 378741-79-8P 378741-80-1P 379266-72-5DP, isomers 379266-72-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction; **melanocortin** receptor agonist prepn. for therapeutic use)
IT 447-53-0, 1,2-Dihydronaphthalene 1189-71-5, Chlorosulfonyl isocyanate 24424-99-5 57292-44-1 115962-35-1 193274-04-3 378741-81-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; **melanocortin** receptor agonist prepn. for therapeutic use)
IT 9004-10-8, Insulin, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sensitizers and mimetics; **melanocortin** receptor agonist prepn. for therapeutic use, and use with other agents)

L15 ANSWER 2 OF 5 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 135:272990 CA
TITLE: Preparation of piperazinylcarbonylaminomethylcarbonylpiperidines as **melanocortin**-4 receptor agonists
INVENTOR(S): Palucki, Brenda L.; Barakat, Khaled J.; Guo, Liangqin; Lai, Yingjie; Nargund, Ravi P.; Park, Min K.; Pollard, Patrick G.; Sebhat, Iyassu K.; Ye, Zhixiong
PATENT ASSIGNEE(S): Merck + Co., Inc., USA
SOURCE: PCT Int. Appl., 220 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001070708	A1	20010927	WO 2001-US8935	20010320

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 2002019523 A1 20020214 US 2001-812965 20010320
PRIORITY APPLN. INFO.: US 2000-191442 P 20000323
US 2000-242265 P 20001020
OTHER SOURCE(S): MARPAT 135:272990
GI



I

AB Title compds. [I; Q = (substituted) (fused) piperazinyl, morpholinyl, thiomorpholinyl; R1 = H, alkyl, (substituted) cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl), etc.; X = (substituted) alkyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl), heterocyclyl(alkyl), cyano(alkyl), aminosulfonyl(alkyl), etc.; Y = H, alkyl, cycloalkyl(alkyl), (substituted) aryl(alkyl), heterocyclyl(alkyl), heteroaryl(alkyl)], were prepd. as **melanocortin**-4 receptor (**MC-4R**) agonists. Thus, capsule formulations contg. title compd. (II) were prepd. Representative I activated **MC-4R** with IC50<1 .mu.M. I are claimed for the treatment of obesity, diabetes, and **sexual dysfunction** including erectile dysfunction and female **sexual dysfunction**.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Preparation of piperazinylcarbonylaminomethylcarbonylpiperidines as **melanocortin**-4 receptor agonists

AB Title compds. [I; Q = (substituted) (fused) piperazinyl, morpholinyl, thiomorpholinyl; R1 = H, alkyl, (substituted) cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl), etc.; X = (substituted) alkyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl), heterocyclyl(alkyl), cyano(alkyl), aminosulfonyl(alkyl), etc.; Y = H, alkyl, cycloalkyl(alkyl), (substituted) aryl(alkyl), heterocyclyl(alkyl), heteroaryl(alkyl)], were prepd. as **melanocortin**-4 receptor (**MC-4R**) agonists. Thus, capsule formulations contg. title compd. (II) were prepd. Representative I activated **MC-4R** with IC50<1 .mu.M. I are claimed for the treatment of obesity, diabetes, and **sexual dysfunction** including erectile dysfunction and female **sexual dysfunction**.

ST piperazinylcarbonylaminomethylcarbonylpiperidine prepn **melanocortin** receptor agonist; **sexual dysfunction** treatment piperazinylcarbonylaminomethylcarbonylpiperidine; obesity treatment piperazinylcarbonylaminomethylcarbonylpiperidine; diabetes treatment piperazinylcarbonylaminomethylcarbonylpiperidine; piperidine piperazinylcarbonylaminomethylcarbonyl prepn

melanocortin receptor agonist

IT Dopamine agonists
(combination therapy; prepn. of piperazinylcarbonylaminomethylcarbonylpiperidines as **melanocortin**-4 receptor agonists)

IT Sulfonylureas
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy; prepn. of piperazinylcarbonylaminomethylcarbonylpiperidines as **melanocortin**-4 receptor agonists)

IT Sexual behavior
(disorder, treatment; prepn. of piperazinylcarbonylaminomethylcarbonylpiperidines as **melanocortin**-4 receptor agonists)

IT Sexual behavior
(impotence, treatment; prepn. of piperazinylcarbonylaminomethylcarbonylpiperidines as **melanocortin**-4 receptor agonists)

IT Pituitary hormone receptors
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(**melanocortin** 4, agonists; prepn. of piperazinylcarbonylaminomethylcarbonylpiperidines as **melanocortin**-4 receptor agonists)

IT Antidiabetic agents
Antiobesity agents
(prepn. of piperazinylcarbonylaminomethylcarbonylpiperidines as **melanocortin**-4 receptor agonists)

IT Adrenoceptor antagonists
(.alpha.2-, combination therapy; prepn. of piperazinylcarbonylaminomethylcarbonylpiperidines as **melanocortin**-4 receptor agonists)

IT Adrenoceptor agonists
(.beta.3-, combination therapy; prepn. of piperazinylcarbonylaminomethylcarbonylpiperidines as **melanocortin**-4 receptor agonists)

IT 171596-29-5, IC-351 171599-83-0, Sildenafil citrate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy; prepn. of piperazinylcarbonylaminomethylcarbonylpiperidines as **melanocortin**-4 receptor agonists)

IT 363187-87-5P 363189-64-4P
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of piperazinylcarbonylaminomethylcarbonylpiperidines as **melanocortin**-4 receptor agonists)

IT 363187-28-4P 363187-29-5P 363187-30-8P 363187-31-9P 363187-32-0P
363187-33-1P 363187-34-2P 363187-35-3P 363187-36-4P 363187-37-5P
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363187-43-3P 363187-44-4P 363187-45-5P 363187-46-6P 363187-47-7P
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363190-13-0P 363190-14-1P 363190-15-2P 363190-16-3P 363190-17-4P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of piperazinylcarbonylaminomethylcarbonylpiperidines as **melanocortin**-4 receptor agonists)

IT 363190-19-6P 363190-59-4P 363190-60-7P 363190-61-8P 363190-62-9P
363190-63-0P 363190-64-1P 363190-65-2P 363190-66-3P 363190-67-4P
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363192-82-9P 363620-30-8P 363620-31-9P 363620-34-2P 363620-36-4P
363620-38-6P 363620-40-0P 363620-41-1P 363620-43-3P 363620-45-5P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of piperazinylcarbonylaminomethylcarbonylpiperidines as **melanocortin**-4 receptor agonists)

IT 75-44-5, Phosgene 75-64-9, tert-Butylamine, reactions 95-89-6, 3-Chloro-2,5-dimethylpyrazine 110-85-0, Piperazine, reactions 124-68-5 535-11-5, Ethyl 2-bromopropionate 556-82-1, 3-Methyl-2-buten-1-ol 565-69-5, Ethyl isopropyl ketone 598-21-0 811-93-8, 1,2-Diamino-2-methylpropane 1067-74-9, Methyl diethylphosphonoacetate 1193-18-6 1436-59-5, cis-1,2-Diaminocyclohexane 2749-11-3, (S)-2-Amino-1-propanol 3674-13-3, Ethyl 2,3-dibromopropionate 5521-55-1, 5-Methyl-2-pyrazinecarboxylic acid 5521-61-9, 6-Methyl-2-pyrazinecarboxylic acid 6294-40-2 7051-34-5, Cyclopropylmethyl bromide 7764-95-6 10316-79-7 20607-43-6, Sodium isopropylsulfide 22059-21-8, 1-Aminocyclopropane-1-carboxylic acid 29460-90-0, 2-Isopropylpyrazine 35761-26-3 45767-66-6, 2-Chloro-4-fluorobenzyl bromide 57292-44-1 57292-45-2 62234-36-0 69555-14-2 83949-32-0 84358-13-4 92329-61-8 129799-15-1 138775-02-7 138775-03-8 139631-62-2, Cyclopropylsulfonyl chloride 142851-03-4 312638-87-2 363192-22-7 363192-64-7 363192-65-8 363192-66-9 363192-73-8 363192-76-1 363192-79-4 363192-81-8 363192-86-3
RL: RCT (Reactant)
(prepn. of piperazinylcarbonylaminomethylcarbonylpiperidines as **melanocortin**-4 receptor agonists)

IT 2435-46-3P 19967-55-6P 29924-70-7P 35761-27-4P 96136-12-8P 126330-92-5P 167262-68-2P 252990-05-9P 278790-00-4P 363189-15-5P 363189-16-6P 363189-17-7P 363189-18-8P 363189-19-9P 363189-20-2P 363189-21-3P 363189-22-4P 363189-23-5P 363189-24-6P 363189-25-7P 363189-26-8P 363189-27-9P 363189-28-0P 363189-29-1P 363189-30-4P 363189-32-6P 363189-34-8P 363189-35-9P 363189-36-0P 363189-37-1P 363189-39-3P 363189-41-7P 363189-43-9P 363189-65-5P 363189-66-6P 363189-67-7P 363189-68-8P 363189-69-9P 363189-70-2P 363189-71-3P 363189-72-4P 363189-73-5P 363189-74-6P 363189-75-7P 363189-76-8P 363189-77-9P 363189-78-0P 363189-79-1P 363189-80-4P 363189-81-5P 363189-82-6P 363189-83-7P 363189-84-8P 363189-85-9P 363189-86-0P 363189-87-1P 363189-88-2P 363190-18-5P 363190-20-9P 363190-21-0P 363190-22-1P 363190-23-2P 363190-24-3P 363190-25-4P 363190-26-5P 363190-27-6P 363190-28-7P 363190-29-8P 363190-30-1P 363190-31-2P 363190-32-3P 363190-33-4P 363190-34-5P 363190-35-6P 363190-36-7P 363190-37-8P 363190-38-9P 363190-39-0P 363190-40-3P 363190-41-4P 363190-42-5P 363190-43-6P 363190-44-7P 363190-45-8P 363190-46-9P 363190-47-0P 363190-48-1P 363190-49-2P 363190-50-5P 363190-51-6P 363190-52-7P 363190-53-8P 363190-54-9P 363190-55-0P 363190-56-1P 363190-57-2P 363190-58-3P 363191-00-8P 363191-01-9P 363191-02-0P 363191-03-1P 363191-04-2P 363191-05-3P 363191-06-4P 363191-10-0P 363191-11-1P 363191-12-2P 363191-14-4P 363191-22-4P 363191-23-5P 363191-24-6P 363191-25-7P 363191-26-8P 363191-27-9P 363191-28-0P 363191-29-1P 363191-74-6P 363191-75-7P 363191-76-8P 363191-77-9P 363191-93-9P 363191-94-0P 363191-95-1P 363191-96-2P 363191-97-3P 363191-98-4P 363191-99-5P 363192-02-3P 363192-03-4P 363192-04-5P 363192-05-6P 363192-07-8P 363192-08-9P 363192-09-0P 363192-10-3P 363192-11-4P 363192-12-5P 363192-13-6P 363192-18-1P 363192-19-2P 363192-20-5P 363192-21-6P 363192-23-8P 363192-24-9P 363192-25-0P 363192-26-1P 363192-27-2P 363192-28-3P 363192-29-4P 363192-30-7P 363192-31-8P 363192-32-9P 363192-33-0P 363192-34-1P 363192-35-2P 363192-36-3P 363192-37-4P 363192-38-5P 363192-39-6P 363192-40-9P 363192-41-0P 363192-42-1P 363192-43-2P 363192-44-3P 363192-45-4P 363192-46-5P 363192-47-6P 363192-48-7P 363192-49-8P 363192-50-1P 363192-51-2P 363192-52-3P 363192-53-4P 363192-54-5P 363192-55-6P 363192-56-7P 363192-57-8P 363192-58-9P 363192-59-0P 363192-60-3P 363192-61-4P 363192-62-5P 363192-63-6P 363192-67-0P 363192-68-1P

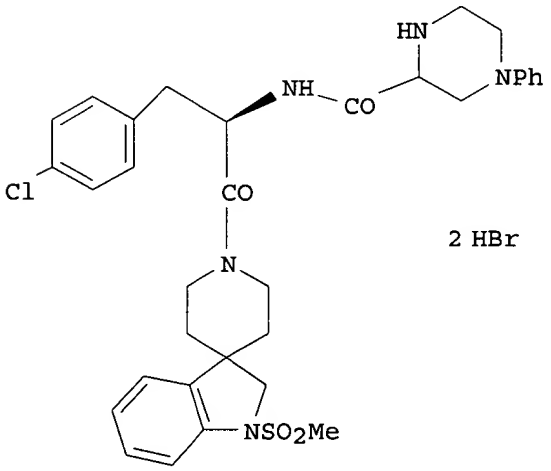
363620-42-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of piperazinylcarbonylaminomethylcarbonylpiperidines as **melanocortin**-4 receptor agonists)

L15 ANSWER 3 OF 5 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 135:267270 CA
TITLE: Spiropiperidine derivatives as **melanocortin** receptor agonists
INVENTOR(S): Palucki, Brenda L.; Nargund, Ravi P.
PATENT ASSIGNEE(S): Merck + Co., Inc., USA
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001070337	A1	20010927	WO 2001-US8833	20010320

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-191669 P 20000323
OTHER SOURCE(S): MARPAT 135:267270
GI



I

AB Certain novel spiropiperidine derivs. are agonists of the human **melanocortin** receptor(s) and, in particular, are selective agonists of the human **melanocortin**-4 receptor (**MC-4R**). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the activation of

MC-4R, such as obesity, diabetes, **sexual dysfunction**, including erectile dysfunction and female **sexual dysfunction**. I was prepd. and pharmacol. tests are described.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Spiropiperidine derivatives as **melanocortin** receptor agonists

AB Certain novel spiropiperidine derivs. are agonists of the human **melanocortin** receptor(s) and, in particular, are selective agonists of the human **melanocortin**-4 receptor (**MC-4R**). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the activation of **MC-4R**, such as obesity, diabetes, **sexual dysfunction**, including erectile dysfunction and female **sexual dysfunction**. I was prepd. and pharmacol. tests are described.

ST spiropiperidine deriv prepn **melanocortin** receptor agonist

IT Sexual behavior
(disorder; spiropiperidine derivs. as **melanocortin** receptor agonists)

IT Sexual behavior
(impotence; spiropiperidine derivs. as **melanocortin** receptor agonists)

IT Pituitary hormone receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**melanocortin**; spiropiperidine derivs. as **melanocortin** receptor agonists)

IT Antidiabetic agents
Antiobesity agents
(spiropiperidine derivs. as **melanocortin** receptor agonists)

IT 128908-32-7, **Melanocortin**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(spiropiperidine derivs. as **melanocortin** receptor agonists)

IT 126937-41-5 138775-03-8
RL: RCT (Reactant)
(spiropiperidine derivs. as **melanocortin** receptor agonists)

IT 126937-42-6P 126937-43-7P 362513-36-8DP, acyl derivs. 362513-73-3P
362513-74-4P 362513-76-6P 362513-77-7P 362513-79-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(spiropiperidine derivs. as **melanocortin** receptor agonists)

IT 362513-35-7P 362513-36-8P 362513-37-9P 362513-38-0P 362513-39-1P
362513-40-4P 362513-41-5P 362513-42-6P 362513-43-7P 362513-44-8P
362513-45-9P 362513-46-0P 362513-47-1P 362513-48-2P 362513-49-3P
362513-50-6P 362513-51-7P 362513-52-8P
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(spiropiperidine derivs. as **melanocortin** receptor agonists)

IT 362513-53-9P 362513-54-0P 362513-55-1P 362513-56-2P 362513-57-3P
362513-58-4P 362513-59-5P 362513-60-8P 362513-61-9P 362513-62-0P
362513-63-1P 362513-64-2P 362513-65-3P 362513-66-4P 362513-67-5P
362513-68-6P 362513-69-7P 362513-70-0P 362513-71-1P 362513-72-2P
362513-78-8P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(spiropiperidine derivs. as **melanocortin** receptor agonists)

L15 ANSWER 4 OF 5 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 134:116238 CA
TITLE: **Melanocortin** receptor-3 ligands to treat **sexual dysfunction**

INVENTOR(S): Dines, Kevin C.; Gahman, Timothy C.; Girten, Beverly E.; Hitchin, Douglas L.; Holme, Kevin R.; Lang, Hengyuan; Slivka, Sandra R.; Watson-Straughan, Karen J.; Tuttle, Ronald R.; Pei, Yazhong
PATENT ASSIGNEE(S): Trega Biosciences, Inc., USA
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005401	A1	20010125	WO 2000-US19408	20000713
W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6284735	B1	20010904	US 1999-356386	19990716

PRIORITY APPLN. INFO.:
US 1999-356386 A2 19990716
US 1999-364825 A2 19990730
US 1999-401004 A2 19990921
US 1998-83368 P 19980428
US 1999-301391 A1 19990428
US 1999-306686 A2 19990506

OTHER SOURCE(S): MARPAT 134:116238
AB Methods for treating **sexual dysfunction**, such as erectile dysfunction or sexual arousal disorder, with a compd. having the generic formula X1-X2-D-Phe-Arg-D-Trp-X3 [X1 = R1R2NCHR3CY1Y2, Ac, H, or absent, where R1 = R2, COPh, CO2Bu-t, CO2CH2Ph, CHCO-(polyethylene glycol) or A which is N,O-(un)substituted 3-amino-4,5,6-trihydroxytetrahydro-2-pyranyl; R2 = H, Ac, Et, PhCH2; R3 = alkyl, cycloalkyl; Y1, Y2 = H or together form carbonyl or thiocarbonyl; X2 = NR1CHR4CY1Y2-His, His, Ac, or H, where R4 = (CH2)mCONH2, (CH2)mCONHR1, or (CH2)CONHA (m = 1-3); X3 = NR1CHR6(CH2)nCY1Y2R5 or R5, where R5 = OH, OR3, NH2, SH, NHMe, NHCH2PH, or A; R6 = H or R3, n = 0-3]. A particularly useful compd. is HP-228, which has the formula Ac-Nle-Gln-His-D-Phe-Arg-D-Trp-Gly-NH2. The invention also provides methods for selecting **melanocortin** receptor-3 ligands by detg. whether a compd. modulates the activity of **MC**-3 as an agonist or antagonist. These methods can be used to screen compd. libraries, including benzimidazoles, for ligands to treat **MC** -3-assocd. conditions. Such conditions include **sexual dysfunction**, including erectile dysfunction and sexual arousal disorder (data given).
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Melanocortin** receptor-3 ligands to treat **sexual dysfunction**

AB Methods for treating **sexual dysfunction**, such as erectile dysfunction or sexual arousal disorder, with a compd. having the generic formula X1-X2-D-Phe-Arg-D-Trp-X3 [X1 = R1R2NCHR3CY1Y2, Ac, H, or absent, where R1 = R2, COPh, CO2Bu-t, CO2CH2Ph, CHCO-(polyethylene glycol) or A which is N,O-(un)substituted 3-amino-4,5,6-trihydroxytetrahydro-2-

pyranyl; R2 = H, Ac, Et, PhCH2; R3 = alkyl, cycloalkyl; Y1, Y2 = H or together form carbonyl or thiocarbonyl; X2 = NR1CHR4CY1Y2-His, His, Ac, or H, where R4 = (CH2)mCONH2, (CH2)mCONHR1, or (CH2)CONHA (m = 1-3); X3 = NR1CHR6(CH2)nCY1Y2R5 or R5, where R5 = OH, OR3, NH2, SH, NHMe, NHCH2PH, or A; R6 = H or R3, n = 0-3]. A particularly useful compd. is HP-228, which has the formula Ac-Nle-Gln-His-D-Phe-Arg-D-Trp-Gly-NH2. The invention also provides methods for selecting **melanocortin** receptor-3 ligands by detg. whether a compd. modulates the activity of **MC**-3 as an agonist or antagonist. These methods can be used to screen compd. libraries, including benzimidazoles, for ligands to treat **MC**-3-assocd. conditions. Such conditions include **sexual dysfunction**, including erectile dysfunction and sexual arousal disorder (data given).

ST peptide prepn **melanocortin** receptor **sexual dysfunction**; benzimidazole combinatorial library **melanocortin** receptor **sexual dysfunction**

IT Sexual behavior
(disorder; **melanocortin** receptor-3 ligands to treat **sexual dysfunction**)

IT Combinatorial library
(**melanocortin** receptor-3 ligands to treat **sexual dysfunction**)

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**melanocortin** receptor-3 ligands to treat **sexual dysfunction**)

IT Pituitary hormone receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**melanocortin**; **melanocortin** receptor-3 ligands to treat **sexual dysfunction**)

IT 172617-89-9P, Hp-228
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**melanocortin** receptor-3 ligands to treat **sexual dysfunction**)

IT 7565-89-1P 170103-02-3P 170103-04-5P 170103-05-6P 182687-55-4P
182687-56-5P 182687-57-6P 182687-58-7P 182687-59-8P 182687-60-1P
182687-61-2P 205499-42-9P 205499-43-0P 223473-41-4P, HP 467
252047-01-1P 252047-02-2P 252047-03-3P 252047-04-4P 252047-05-5P
252047-06-6P 252047-09-9P 252047-10-2P 252047-11-3P 252047-12-4P
252047-13-5P 321180-15-8P 321180-17-0P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**melanocortin** receptor-3 ligands to treat **sexual dysfunction**)

IT 248947-36-6 321180-43-2 321180-45-4 321180-47-6 321180-49-8
321180-51-2 321180-53-4 321180-55-6 321180-57-8 321180-59-0
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**melanocortin** receptor-3 ligands to treat **sexual dysfunction**)

L15 ANSWER 5 OF 5 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 134:42445 CA
TITLE: Preparation of piperidine amino acid derivatives as **melanocortin**-4 receptor agonists

INVENTOR(S): Bakshi, Raman K.; Barakat, Khaled J.; Nargund, Ravi P.; Palucki, Brenda L.; Patchett, Arthur A.; Sebhat, Iyassu; Ye, Zhixiong; Van, Der Ploeg Leonardus H. T.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Van Der Ploeg, Leonardus H. T.
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000074679	A1	20001214	WO 2000-US14930	20000531
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6350760	B1	20020226	US 2000-585111	20000601

PRIORITY APPLN. INFO.: US 1999-137477 P 19990604
US 1999-169209 P 19991202

OTHER SOURCE(S): MARPAT 134:42445
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Piperidine derivs. I [R2C2 = aryl, 5- or 6-membered heteroaryl or heterocyclyl, 5- to 7-membered carbocyclyl, which may be substituted; L = (CRb2)m, where Rb = H, alkyl, (CH2)n-cycloalkyl or -aryl; m = 0-2, n = 0-3; X, Y = (CH2)0-2; Ra = H, alkyl, (CHRb)n-cycloalkyl, -aryl, -heteroaryl, -O(CHRb)naryl, which may be substituted; Re = H, alkyl, (CH2)n-aryl, -cycloalkyl, -heteroaryl, which may be substituted, acyl, sulfonyl, etc.; R1 = H, alkyl, (CH2)n-cycloalkyl, -aryl, -heteroaryl, -heterocyclyl; R2 = any group given for R1, CN, (CH2)n-carboxamido, -carboxy, -acylamino, sulfonylamino, -amino, etc.] were prepd. as agonists of the human **melanocortin** receptors, in particular, the human **melanocortin**-4 receptor (**MC-4R**). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the activation of **MC-4R**, such as obesity, diabetes, **sexual dysfunction**, including erectile dysfunction and female **sexual dysfunction**. Thus, II trifluoroacetate, prepd. by coupling of Et 1-(D-4-chlorophenylalanyl)-4-cyclohexyl-4-[(1,2,4-triazol-1-yl)methyl]piperidine trifluoroacetate (prepn. given) with N-tert-butoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Boc-D-Tic), was > 2,200-fold, > 10,000-fold, and > 580-fold selective for the human **MC-4R** over human **MC-1R**, **MC-2R**, and **MC-3R**, resp.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Preparation of piperidine amino acid derivatives as **melanocortin**-4 receptor agonists

AB Piperidine derivs. I [R2C2 = aryl, 5- or 6-membered heteroaryl or heterocyclyl, 5- to 7-membered carbocyclyl, which may be substituted; L = (CRb2)m, where Rb = H, alkyl, (CH2)n-cycloalkyl or -aryl; m = 0-2, n = 0-3; X, Y = (CH2)0-2; Ra = H, alkyl, (CHRb)n-cycloalkyl, -aryl, -heteroaryl, -O(CHRb)naryl, which may be substituted; Re = H, alkyl, (CH2)n-aryl, -cycloalkyl, -heteroaryl, which may be substituted, acyl, sulfonyl, etc.; R1 = H, alkyl, (CH2)n-cycloalkyl, -aryl, -heteroaryl, -heterocyclyl; R2 = any group given for R1, CN, (CH2)n-carboxamido, -carboxy, -acylamino, sulfonylamino, -amino, etc.] were prepd. as agonists of the human **melanocortin** receptors, in particular, the human **melanocortin**-4 receptor (**MC-4R**). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the activation of **MC-4R**, such as obesity, diabetes, **sexual dysfunction**, including erectile dysfunction and female **sexual dysfunction**. Thus, II trifluoroacetate, prepd. by coupling of Et 1-(D-4-chlorophenylalanyl)-4-cyclohexyl-4-[(1,2,4-triazol-1-yl)methyl]piperidine trifluoroacetate (prepn. given) with N-tert-butoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Boc-D-Tic), was > 2,200-fold, > 10,000-fold, and > 580-fold selective for the human **MC-4R** over human **MC-1R**, **MC-2R**, and **MC-3R**, resp.

ST piperidine amino acid prepn **melanocortin** receptor agonist

IT Sexual behavior
(disorder; prepn. of piperidine amino acid derivs. as **melanocortin**-4 receptor agonists)

IT Sexual behavior
(impotence; prepn. of piperidine amino acid derivs. as **melanocortin**-4 receptor agonists)

IT Pituitary hormone receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**melanocortin** 4; prepn. of piperidine amino acid derivs. as **melanocortin**-4 receptor agonists)

IT Antidiabetic agents
Antiobesity agents
(prepn. of piperidine amino acid derivs. as **melanocortin**-4 receptor agonists)

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of piperidine amino acid derivs. as **melanocortin**-4 receptor agonists)

IT Dopamine receptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(prepn. of piperidine amino acid derivs. as **melanocortin**-4 receptor agonists)

IT Adrenoceptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(.alpha.2; prepn. of piperidine amino acid derivs. as **melanocortin**-4 receptor agonists)

IT Adrenoceptors
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(.beta.3; prepn. of piperidine amino acid derivs. as **melanocortin**-4 receptor agonists)

IT 312637-61-9P 312637-63-1P 312637-77-7P 312637-91-5P 312638-30-5P
RL: BAC (Biological activity or effector, except adverse); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of piperidine amino acid derivs. as **melanocortin**-4

receptor agonists)

IT 312637-47-1P 312637-48-2P 312637-49-3P 312637-51-7P 312637-53-9P
312637-55-1P 312637-57-3P 312637-59-5P 312637-64-2P 312637-65-3P
312637-66-4P 312637-67-5P 312637-68-6P 312637-70-0P 312637-72-2P
312637-73-3P 312637-75-5P 312637-79-9P 312637-81-3P 312637-82-4P
312637-83-5P 312637-85-7P 312637-87-9P 312637-89-1P 312637-90-4P
312637-92-6P 312637-93-7P 312637-94-8P 312637-95-9P 312637-96-0P
312637-97-1P 312637-98-2P 312637-99-3P 312638-00-9P 312638-02-1P
312638-04-3P 312638-06-5P 312638-08-7P 312638-10-1P 312638-11-2P
312638-13-4P 312638-15-6P 312638-17-8P 312638-19-0P 312638-21-4P
312638-23-6P 312638-24-7P 312638-26-9P 312638-28-1P 312638-29-2P
312638-32-7P 312638-33-8P 312638-35-0P 312638-36-1P 312638-37-2P
312638-38-3P 312638-40-7P 312638-42-9P 312638-44-1P 312638-46-3P
312638-47-4P 312638-48-5P 312638-49-6P 312638-50-9P 312638-52-1P
312638-54-3P 312638-56-5P 312638-58-7P 312638-59-8P 312638-60-1P
312638-61-2P 312638-62-3P 312638-63-4P 312638-64-5P 312638-65-6P
312638-66-7P 312638-67-8P 312638-69-0P 312638-70-3P 312638-71-4P
312638-72-5P 312638-73-6P 312638-74-7P 312638-75-8P 312638-77-0P
312638-79-2P 312638-81-6P 312639-64-8P 312639-65-9P 312639-66-0P
312639-67-1P 312639-68-2P 312639-69-3P 312639-70-6P 312639-71-7P
312639-72-8P 312639-73-9P 312639-75-1P 312639-76-2P 312639-77-3P
312639-78-4P 312639-80-8P 312639-82-0P 312639-83-1P 312639-84-2P
312639-85-3P 312639-87-5P 312639-88-6P 312639-89-7P 312639-90-0P
312639-91-1P 312639-92-2P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of piperidine amino acid derivs. as **melanocortin**-4 receptor agonists)

IT 57-88-5, Cholesterol, biological studies 9001-42-7, .alpha.-Glucosidase 9028-35-7, HMG-CoA reductase 82785-45-3, Neuropeptide y
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(prepn. of piperidine amino acid derivs. as **melanocortin**-4 receptor agonists)

IT 312639-52-4P 312639-53-5P
RL: PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of piperidine amino acid derivs. as **melanocortin**-4 receptor agonists)

IT 542-69-8, Butyl iodide 24465-45-0 29364-29-2, Sodium 2-methyl-2-propanethiolate 29943-42-8, Tetrahydro-4H-pyran-4-one 31637-11-3 41253-21-8, 1,2,4-Triazole sodium salt 57292-44-1 115962-35-1 136465-81-1 142851-03-4 150417-15-5 167262-68-2 207342-56-1 273378-16-8
RL: RCT (Reactant)
(prepn. of piperidine amino acid derivs. as **melanocortin**-4 receptor agonists)

IT 10462-00-7P 115238-58-9P 142001-86-3P 158144-85-5P 188916-68-9P
225240-55-1P 252008-88-1P 312638-82-7P 312638-83-8P 312638-84-9P
312638-86-1P 312638-87-2P 312638-88-3P 312638-89-4P 312638-91-8P
312638-93-0P 312638-94-1P 312638-95-2P 312638-96-3P 312638-97-4P
312638-98-5P 312638-99-6P 312639-00-2P 312639-01-3P 312639-02-4P
312639-03-5P 312639-04-6P 312639-06-8P 312639-08-0P 312639-09-1P
312639-11-5P 312639-12-6P 312639-13-7P 312639-14-8P 312639-15-9P
312639-16-0P 312639-17-1P 312639-18-2P 312639-19-3P 312639-20-6P
312639-21-7P 312639-22-8P 312639-23-9P 312639-24-0P 312639-25-1P
312639-26-2P 312639-27-3P 312639-28-4P 312639-29-5P 312639-30-8P
312639-31-9P 312639-32-0P 312639-33-1P 312639-34-2P 312639-35-3P
312639-36-4P 312639-37-5P 312639-38-6P 312639-39-7P 312639-40-0P
312639-41-1P 312639-42-2P 312639-43-3P 312639-44-4P 312639-45-5P

312639-46-6P 312639-47-7P 312639-48-8P 312639-49-9P 312639-50-2P
312639-51-3P 312639-54-6P 312639-55-7P 312639-56-8P 312639-57-9P
312639-58-0P 312639-59-1P 312639-60-4P 312639-61-5P 312639-62-6P
312639-63-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of piperidine amino acid derivs. as **melanocortin**-4 receptor agonists)

IT 9004-10-8D, Insulin, mimetic
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of piperidine amino acid derivs. as **melanocortin**-4 receptor agonists)

IT 9025-82-5, Phosphodiesterase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(type V cyclic-GMP-selective phosphodiesterase inhibitor; prepn. of piperidine amino acid derivs. as **melanocortin**-4 receptor agonists)

=> D HIS

(FILE 'HOME' ENTERED AT 14:31:56 ON 26 FEB 2002)

FILE 'CA' ENTERED AT 14:32:02 ON 26 FEB 2002
L1 454 S SEX? DYSFUNC?
L2 862 S MELANOCORTIN?
L3 10 S MC-4R
L4 6 S MC-1R
L5 69 S MC4R
L6 117 S MC1R
L7 39 S MC3R OR MC-3R
L8 26945 S MC
L9 18 S MC5R OR MC-5R
L10 25 S MC2R OR MC-2R
L11 421 S MC!R
L12 27341 S L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11
L13 5 S L12 AND L1
L14 282 S L12 AND L2
L15 5 S L13 AND L14

=> S L14 NOT L15
L16 277 L14 NOT L15

=> S L1 AND L2
L17 12 L1 AND L2

=> S L17 NOT L15
L18 7 L17 NOT L15

=> D IBIB ABS 1-7

L18 ANSWER 1 OF 7 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 136:96099 CA
TITLE: Treatment of male **sexual dysfunction**
INVENTOR(S): Naylor, Alasdair Mark; Van der Graaf, Pieter Hadewijn; Wayman, Christopher Peter
PATENT ASSIGNEE(S): Pfizer Limited, UK; Pfizer Inc.
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002003995	A2	20020117	WO 2001-IB1187	20010702

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2000-16684 A 20000706
GB 2000-30647 A 20001215
GB 2001-6167 A 20010313
GB 2001-8483 A 20010404

OTHER SOURCE(S): MARPAT 136:96099

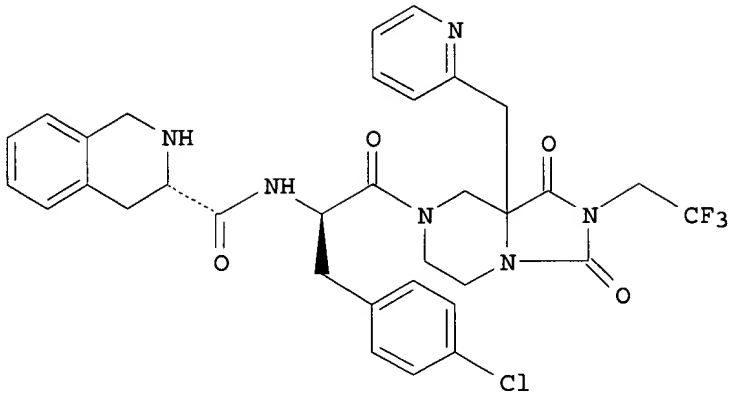
AB The present invention relates to the use of neutral endopeptidase inhibitors (NEPi) and a combination of NEPi and phosphodiesterase type (PDE5) inhibitor for the treatment of male **sexual dysfunction**, in particular MED.

L18 ANSWER 2 OF 7 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 136:69824 CA
TITLE: Preparation of heterocycle compounds as **melanocortin** receptor ligands
INVENTOR(S): Carpino, Philip Albert; Cole, Bridget McCarthy; Morgan, Bradley Paul
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 108 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002000654	A1	20020103	WO 2001-IB995	20010531

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-214616 P 20000628
OTHER SOURCE(S): MARPAT 136:69824
GI



II

AB Compds. represented by formula HET-COCR3R4-NX4-CO(CR6R7)m-D [I; wherein m = 0, 1 or 2; HET = heterocyclyl; R3, R4 = H,, C1-8 alkyl, CH(R8)-aryl, -CH(R8)-heteroaryl, -C0-3 alkyl-C3-8 cycloalkyl (wherein the aryl or heteroaryl groups are optionally substituted by one or two groups; R8 = H, C1-8 alkyl, -C0-3 alkylaryl, -C0-3 alkylheteroaryl, -C3-6 cycloalkyl); R6, R7 = H, C1-6 alkyl, -C0-3 alkyl-aryl, -C0-3 alkyl-heteroaryl, -C0-3 alkyl-C3-8 cycloalkyl; or R6 and R7 together with the nitrogen atom to which they are attached form a 5- or 6-membered ring optionally contg. an addnl. heteroatom selected from O, S, NR3; D = -C0-6 alkylamino-C(:NR7)-NR15R16, -C0-6 alkylaminopyridyl, -C0-6 alkylaminoimidazolyl, -C0-6 alkylaminothiazolyl, -C0-6 alkylaminopyrimidinyl, -C0-6 alkylaminopiperazinyl-R15, -C0-6 alkylmorpholinyl, etc. (wherein R15, R16 = H, -C1-6 alkyl, -C0-3 alkylaryl, -C0-3 alkylheteroaryl, or -C0-3 alkyl-C3-8 cycloalkyl, wherein the alkyl and aryl groups are optionally substituted with one or two groups); X4 = H or C1-6 alkyl or X4 is taken together with R4 and the nitrogen atom to which X4 is attached and the carbon atom to which R4 is attached and form a five to seven membered ring] are prepd. **Melanocortins** are peptides derived from pro-opiomelanocortins (POMC) that bind to and activate G-protein coupled receptors (GPCR's) of the **melanocortin** receptor family and regulate a diverse no. of physiol. processes including food intake., metab., and thermogenesis as well as **sexual dysfunction**. These compds. I are useful for the treatment or prevention of disorders, diseases, or conditions responsive to the activation of **melanocortin** receptor including obesity, diabetes mellitus, male or female **sexual dysfunction**, erectile dysfunction, or disorders that cause redn. in appetite, or feeding behavior and/or body wt.; for modulating appetite and metabolic rates; for acutely stimulating the appetite for the treatment of hepatic lipidosis, cachexia, and other pathologies resulting in/from inappropriate food intake and wt. loss; for acutely stimulating the appetite of livestock for the treatment of ketosis, postpartum anestrus, and other metabolic and reproductive pathologies resulting in/from inappropriate food intake and wt. loss; and for enhancing growth and survivability of neonates in livestock. Thus, esterification of N-Boc-L-Tic-OH with N-hydroxysuccinimide using Et3N and EDC in CH2Cl2 at room temp. for 4 h gave 3,4-Dihydro-1H-isoquinoline-2,3-(S)-dicarboxylic acid 2-tert-Bu ester 3-(2,5-dioxopyrrolidin-1-yl) ester which was condensed with D-p-chlorophenylalanine in the presence of Et3N in CH2Cl2 at room temp. overnight to give 3-(S)-[(R)-1-Carboxy-2-(4-chlorophenyl)ethylcarbamoyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-Bu ester. The latter compd. was further condensed with 8a-(Pyridin-2-ylmethyl)-2-(2,2,2-trifluoroethyl)tetrahydroimidazo[1,5-

a]pyrazine-1,3-dione using Et3N and EDC in CH2Cl2 at 0.degree. for 5 h to give (S)-3-[(R)-1-(4-Chlorobenzyl)-2-[1,3-dioxo-8a-(pyridin-2-ylmethyl)-2-(2,2,2-trifluoroethyl)hexahydroimidazo[1,5-a]pyrazin-7-yl]-2-oxoethylcarbamoyl]-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-Bu ester which was treated with a mixt. of EtOH and concd. HCl at 0.degree. for 0.5 h to give (S)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid N-[(R)-1-(4-chlorobenzyl)-2-[1,3-dioxo-8a-(pyridin-2-ylmethyl)-2-(2,2,2-trifluoroethyl)hexahydroimidazo[1,5-a]pyrazin-7-yl]-2-oxoethyl]amide (II) hydrochloride which may be considered as a dipeptide analog hepterocycle amide, N-[N-(L-1,2,3,4-Tetrahydroisoquinoline-3-carbonyl)-D-p-chlorophenylalanyl]-1,3-dioxo-8a-(pyridin-2-ylmethyl)-2-(2,2,2-trifluoroethyl)hexahydroimidazo[1,5-a]pyrazine.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 3 OF 7 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 135:314399 CA
TITLE: Detection of variations in the DNA methylation profile of genes in the determining the risk of disease
INVENTOR(S): Berlin, Kurt; Piepenbrock, Christian; Olek, Alexander
PATENT ASSIGNEE(S): Epigenomics A.-G., Germany
SOURCE: PCT Int. Appl., 636 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 37
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001077373	A2	20011018	WO 2001-DE1486	20010406
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 10019058	A1	20011220	DE 2000-10019058	20000406
WO 2001077373	A2	20011018	WO 2001-XA1486	20010406
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, CF, CG, CI, CM, GA, GW, ML, MR, NE, SN, TD, TG				
WO 2001077373	A2	20011018	WO 2001-XB1486	20010406
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,				

CF, CG, CI, CM, GA, GW, ML, MR, NE, SN, TD, TG
WO 2001077373 A2 20011018 WO 2001-XC1486 20010406
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, CF, CG, CI, CM, GA, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: DE 2000-10019058 A 20000406
WO 2001-DE1486 W 20010406

AB The invention relates to an oligonucleotide kit as probe for the detection of relevant variations in the DNA methylation of a target group of genes. The invention further relates to the use of the same for detg. the gene variant with regard to DNA methylation, a medical device, using an oligonucleotide kit, a method for detg. the methylation state of an individual and a method for the establishment of a model for establishing the probability of onset of a disease state in an individual. Such diseases may be: undesired pharmaceutical side-effects; cancerous diseases; CNS dysfunctions, injuries or diseases; aggressive symptoms or relational disturbances; clin., psychol. and social consequences of brain injury; psychotic disorders and personality disorders; dementia and/or assocd. syndromes; cardiovascular disease, dysfunction and damage; dysfunction, damage or disease of the gastrointestinal tract; dysfunction, damage or disease of the respiratory system; injury, inflammation, infection, immunity and/or anastasis; dysfunction, damage or disease of the body as an abnormal development process; dysfunction, damage or disease of the skin, muscle, connective tissue or bones; endocrine and metabolic dysfunction, damage or disease; headaches or **sexual dysfunction**. This abstr. record is one of several records for this document necessitated by the large no. of index entries required to fully index the document and publication system constraints.

L18 ANSWER 4 OF 7 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 135:205579 CA
TITLE: HP-3228 and related peptides to treat **sexual dysfunction**
INVENTOR(S): Girten, Beverly E.; Tuttle, Ronald R.
PATENT ASSIGNEE(S): Lion Bioscience A.-G., Germany
SOURCE: U.S., 12 pp., Cont.-in-part of U.S. Ser. No. 306,686.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6284735	B1	20010904	US 1999-356386	19990716
US 6127381	A	20001003	US 1999-301391	19990428
WO 2001005401	A1	20010125	WO 2000-US19408	20000713

W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1998-83368 P 19980428
US 1999-301391 A1 19990428
US 1999-306686 A2 19990506
US 1999-356386 A2 19990716
US 1999-364825 A2 19990730
US 1999-401004 A2 19990921

OTHER SOURCE(S): MARPAT 135:205579

AB Methods for treating erectile dysfunction in males and **sexual dysfunction**, such as sexual arousal disorder, in females. The methods involve administering an effective amt. of certain compds. such as HP-228 (Ac-Nle-Gln-His(D)Phe-Arg-(D)Trp-Gly-NH2).

REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 5 OF 7 CA COPYRIGHT 2002 ACS

ACCESSION NUMBER: 135:175427 CA

TITLE: Uses of agrp-**melanocortin** receptor binding modulating compounds

INVENTOR(S): Hadcock, John Richard Neville; Swick, Andrew Gordon

PATENT ASSIGNEE(S): Pfizer Products Inc., USA

SOURCE: Eur. Pat. Appl., 23 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1125579	A2	20010822	EP 2001-300233	20010111
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 2001000106	A	20010828	BR 2001-106	20010118
JP 2001242173	A2	20010907	JP 2001-9643	20010118

PRIORITY APPLN. INFO.: US 2000-176508 P 20000118
US 2000-206126 P 20000522

AB The present invention provides a method of treating obesity, **sexual dysfunction** (including erectile dysfunction), diabetes, insulin resistance, hyperinsulinemia, Syndrome X, adrenal dysfunction, hypertension, hypercholesterolemia, atherosclerosis, hyperlipoproteinemia, hypertriglyceridemia, or substance abuse, the method comprising the step of administering to a patent having or at risk of having one of the above-mentioned diseases a therapeutically effective amt. of a compd. that attenuates the binding of agouti-related protein to **melanocortin** receptors, but does not attenuate the binding of .alpha.-MSH to **melanocortin** receptors. The present invention also provides a method of identifying a compd. that is useful for the treatment or prevention of obesity, **sexual dysfunction** (including erectile dysfunction), diabetes, insulin resistance, hyperinsulinemia, Syndrome X, adrenal dysfunction, hypertension, hypercholesterolemia, atherosclerosis, hyperlipoproteinemia, hypertriglyceridemia, or substance abuse, the method comprising the steps of: (1) detg. if a compd. affects the binding of agouti-related protein to **melanocortin** receptors; (2) detg. if a compd. affects the binding of .alpha.-MSH to **melanocortin** receptors; and (3) selecting a compd. that attenuates the binding of agouti-related protein to **melanocortin** receptors, but does not affect the binding of

.alpha.-MSH to **melanocortin** receptors.

L18 ANSWER 6 OF 7 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 134:76409 CA
TITLE: Compositions and methods for treatment of **sexual dysfunction**
INVENTOR(S): Blood, Christine H.; Shadiack, Annette M.; Bernstein, Joanna K.; Herbert, Guy W.
PATENT ASSIGNEE(S): Palatin Technologies Inc., USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000224	A1	20010104	WO 2000-US18217	20000629

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-142346 P 19990629
US 2000-194987 P 20000405
US 2000-606501 A 20000628

AB Compns. and methods are provided for the treatment of **sexual dysfunctions** in mammals, such as erectile dysfunction and female **sexual dysfunction**. In one embodiment, a peptide-based compn. including the peptide sequence Ac-Nle-cyclo(-Asp-His-D-Phe-Arg-Trp-Lys)-OH is administered. Methods of administration include injection, oral, nasal and mucosal administration.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L18 ANSWER 7 OF 7 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 132:22957 CA
TITLE: Preparation of spiropiperidine derivatives as **melanocortin** receptor agonists
INVENTOR(S): Nargund, Ravi P.; Ye, Zhixiong; Palucki, Brenda L.; Bakshi, Raman K.; Patchett, Arthur A.; Van Der Ploeg, Leonardus H. T.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9964002	A1	19991216	WO 1999-US13252	19990610

W: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV,

MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR,
TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

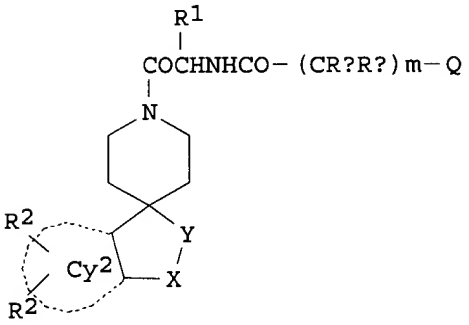
AU 9946801	A1	19991230	AU 1999-46801	19990610	
EP 1085869	A1	20010328	EP 1999-930220	19990610	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO					
US 6294534	B1	20010925	US 1999-329814	19990610	
US 2001029259	A1	20011011	US 2001-781373	20010212	

PRIORITY APPLN. INFO.:

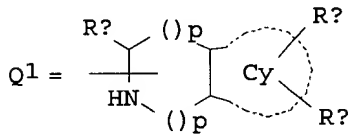
US 1998-88908	P	19980611
GB 1998-17179	A	19980806
US 1999-123260	P	19990308
US 1999-329814	A3	19990610
WO 1999-US13252	W	19990610

OTHER SOURCE(S): MARPAT 132:22957

GI



I



AB Certain novel spiropiperidine compds. I [Cy2 = six-membered arom. ring contg. 0 or 1 N; X = O, CH2, etc.; Q = Q1; Y = CO, SO2, etc; R1, Rb = H, C1-8 alkyl, etc.; R2 = H or halo; Rc = Rb, halo, ORb, NHSO2Rb, N(Rb)2, SO2Rb, CF3, OCF3; Cy = aryl, 5 or 6 membered heteroaryl, 5 or 6 membered heterocyclyl, 5 or 6 membered carbocyclyl; m, p, q independently = 0, 1, or 2] are agonists of **melanocortin** receptors (no data) and are useful for the treatment, control or prevention of diseases and disorders responsive to the activation of **melanocortin** receptors. The compds. of the present invention are therefore useful for treatment of diseases and disorders such as obesity, diabetes, **sexual dysfunction** including erectile dysfunction and female **sexual dysfunction**.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> D IBIB ABS 1-17

L22 ANSWER 1 OF 17 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 133:145447 CA
TITLE: Methods and reagents for discovering and using mammalian **melanocortin** receptor agonists and antagonists to modulate feeding behavior in animals
INVENTOR(S): Cone, Roger D.; Fan, Wei; Boston, Bruce A.; Kesterton, Robert A.; Lu, Dongsi; Chen, Wenbiao
PATENT ASSIGNEE(S): Oregon Health Sciences University, USA
SOURCE: U.S., 82 pp., Cont.-in-part of U.S. 5,849,871.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
US 6100048	A	20000808	US 1996-706281	19960904	✓
US 5280112	A	19940118	US 1992-866560	19920410	<--
US 5837521	A	19981117	US 1993-44812	19930408	<--
US 5849871	A	19981215	US 1995-466906	19950606	<--
US 5773229	A	19980630	US 1995-478992	19950607	<--
WO 9810068	A2	19980312	WO 1997-US15565	19970904	<--
WO 9810068	A3	19980625			
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
AU 9741812	A1	19980326	AU 1997-41812	19970904	<--
AU 719954	B2	20000518			
EP 935655	A1	19990818	EP 1997-939799	19970904	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2001510984	T2	20010807	JP 1998-512888	19970904	
US 6278038	B1	20010821	US 1998-97231	19980612	
US 6046011	A	20000404	US 1998-105298	19980626	
US 6268221	B1	20010731	US 1998-201746	19981201	

PRIORITY APPLN. INFO.:

US 1992-866560	A3	19920410
US 1992-886979	A3	19920410
US 1993-44812	A2	19930408
US 1995-466906	A2	19950606
US 1995-478992	A2	19950607
US 1992-866979	A3	19920410
US 1993-77673	A3	19930615
US 1996-706281	A	19960904
US 1997-50063	P	19970613
WO 1997-US15565	W	19970904

AB The present invention provides recombinant expression constructs comprising nucleic acid encoding mammalian **melanocortin** receptors, and mammalian cells into which said recombinant expression constructs have been introduced that express functional mammalian

melanocortin receptors. The invention provides a panel of such transformed mammalian cells expressing **melanocortin** receptors for screening compds. for receptor agonist and antagonist activity. The invention also provides methods for using such panels of **melanocortin** receptor-expressing mammalian cells to specifically detect and identify agonists and antagonists for each **melanocortin** receptor, as well as patterns of agonist and antagonist activity of said compds. for the class of **melanocortin** receptors. Such screening methods provide a means for identifying compds. with patterns of **melanocortin** agonist and antagonist activity which are assocd. with the capacity to influence or modify metab. and behavior, particularly feeding behavior.

REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 2 OF 17 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:61608 CA
TITLE: Cells expressing mammalian **melanocortin** receptors for **drug** screening and transgenic animals with receptor gene knockout
INVENTOR(S): Cone, Roger D.; Chen, Wenbiao; Low, Malcolm J.
PATENT ASSIGNEE(S): Oregon Health Sciences University, USA
SOURCE: PCT Int. Appl., 144 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 9856914	A1	19981217	WO 1998-US12098	19980612	<--
W: AU, CA, JP					
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
AU 9879595	A1	19981230	AU 1998-79595	19980612	<--

PRIORITY APPLN. INFO.: US 1997-50063 P 19970613
WO 1998-US12098 W 19980612

AB This invention provides methods and reagents for developing naturally-occurring and synthetic agonists and antagonists specific for a mammalian **melanocortin** receptor such as MC5-R. Also provided by the invention are nucleic acids, constructs, vectors and methods for producing an animal bearing a genetically-disrupted endogenous M5C-R **melanocortin** receptor, in both the heterozygous and homozygous condition. The cDNAs for mouse and human MC1-R, bovine and human MC2-R, rat MC3-R, human MC4-R and mouse MC5-R were cloned and expressed in mammalian cells, e.g., 293 or mouse Y1 cells, and the ligand binding characteristics were detd. MC5-R knockout mice were also prepd. and the consequences of this knockout were detd. Thus, MC5-R was found to regulate protein secretion by the lacrimal gland. MC5-R was also shown to be required for porphyrin prodn. in the Harderian gland.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 3 OF 17 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:48845 CA
TITLE: Biochemical, Biophysical, and **Pharmacological** Characterization of Bacterially Expressed Human Agouti-Related Protein
AUTHOR(S): Rosenfeld, Robert D.; Zeni, Lisa; Welcher, Andrew A.;

Narhi, Linda O.; Hale, Clarence; Marasco, Julie; Delaney, John; Gleason, Thomas; Philo, John S.; Katta, Viswanathan; Hui, John; Baumgartner, Jamie; Graham, Melissa; Stark, Kevin L.; Karbon, William
CORPORATE SOURCE: Amgen Inc., Thousand Oaks, CA, 91320-1789, USA
SOURCE: Biochemistry (**1998**), 37(46), 16041-16052
CODEN: BICHAW; ISSN: 0006-2960
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The agouti-related protein gene (Agrp) is a novel gene implicated in the control of feeding behavior. The hypothalamic expression of Agrp is regulated by leptin, and overexpression of Agrp in transgenic animals results in obesity and diabetes. By analogy with the known actions of agouti, these data suggest a role for the Agrp gene product in the regulation of **melanocortin** receptors expressed in the central nervous system. The availability of recombinant, highly purified protein is required to fully address this potential interaction. A nearly full-length form of AGRP (MKd5-AGRP) was expressed in the cytosolic or sol. fraction of Escherichia coli and appeared as large intermol. disulfide-bonded aggregates. Following oxidn., refolding, and purifn., this protein was sol., and eluted as a single sym. peak on RP-HPLC. CD studies indicated that the purified protein contains primarily random coil and .beta.-sheet secondary structure. Sedimentation velocity studies at neutral pH demonstrated that MKd5-AGRP is monomeric at low micromolar concns. Mobility shifts obsd. using SDS-PAGE under reducing and nonreducing conditions for bacterially expressed and mammalian expressed AGRP were identical, an indication of a similar disulfide structure. The purifn. to homogeneity of a second, truncated form of AGRP (Md65-AGRP) which was expressed in the insol. or inclusion body fraction is also described. Both forms act as competitive antagonists of .alpha.-MSH at **melanocortin**-3 (**MC**-3) and **melanocortin**-4 receptors (**MC**-4). The demonstration that AGRP is an endogenous antagonist with respect to these receptors is a unique mechanism within the central nervous system, and has important implications in the control of feeding.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 4 OF 17 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:11781 CA
TITLE: Nucleic acids encoding the .gamma.-msh receptor mc3-r
INVENTOR(S): Cone, Roger D.; Roselli-Rehfuss, Linda; Mountjoy, Kathleen G.; Robbins, Linda S.
PATENT ASSIGNEE(S): State of Oregon, USA
SOURCE: U.S., 21 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
US 5837521	A	19981117	US 1993-44812	19930408	<--
US 5994087	A	19991130	US 1995-475637	19950607	
US 6100048	A	20000808	US 1996-706281	19960904	
US 6278038	B1	20010821	US 1998-97231	19980612	
US 6261838	B1	20010717	US 1998-191359	19981113	

PRIORITY APPLN. INFO.: US 1992-866560 A3 19920410

US 1992-886979	A3	19920410
US 1993-44812	A3	19930408
US 1993-77673	A3	19930615
US 1995-466906	A2	19950606
US 1995-478992	A2	19950607
US 1996-706281	A2	19960904
US 1997-50063	P	19970613

AB The present invention relates to a mammalian **melanocortin** receptor. The invention is directed toward the isolation, characterization and **pharmacol**. use of a mammalian **melanocortin** receptor (MC3-R). The invention specifically provides a particular **melanocortin** receptor, termed MC3-R, isolated as a complementary DNA copy of mRNA corresponding to the gene for this receptor in rats. Also provided is a eukaryotic recombinant expression construct capable of expressing a mammalian **melanocortin** receptor in cultures of transformed eukaryotic cells and such cultures of transformed eukaryotic cells that synthesize a mammalian **melanocortin** receptor. The invention also provides methods for screening in vitro agonists and antagonists of such a **melanocortin** receptor using prepns. of receptor protein from such cultures of eukaryotic cells transformed with a recombinant expression construct.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 5 OF 17 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:578 CA
TITLE: Solution structures of the melanocyte-stimulating hormones by two-dimensional NMR spectroscopy and dynamical simulated-annealing calculations
AUTHOR(S): Lee, Jung-Hoon; Lim, Sung-Kil; Huh, Sung-Ho; Lee, Donghan; Lee, Weontae
CORPORATE SOURCE: Department of Biochemistry, College of Science, Yonsei University, Seoul, 120-740, S. Korea
SOURCE: Eur. J. Biochem. (**1998**), 257(1), 31-40
CODEN: EJBCAI; ISSN: 0014-2956
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Melanocortins**, which are involved in melanocyte pigmentation control and glucocorticoid stimulation, have functional roles in various physiol. mechanisms and have been shown to participate in higher cortical functions. Recently, it has also been reported that MSH and **melanocortin** 4 receptor (**MC4R**) are the key components of the hypothalamic response to obesity. The soln. structures of both .alpha.-MSH (Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH2) and its analog .alpha.-MSH-ND (Ac-Ahx-Asp-His-DPhe-Arg-Trp-Lys-NH2) (Ahx, 2-aminohexanoic acid) have been detd. by two-dimensional NMR spectroscopy and simulated-annealing calcns. The NMR data revealed that .alpha.-MSH forms a hairpin loop conformation which includes conserved message sequences, whereas .alpha.-MSH-ND prefers a type I .beta.-turn comprising residues of Asp2-His3-DPhe4-Arg5. Final simulated-annealing structures of both .alpha.-MSH-ND and .alpha.-MSH peptides converged with rmsd of 0.07 nm for .alpha.-MSH-ND and 0.1 nm for .alpha.-MSH between backbone atoms, resp. This result will provide the structural bases of **melanocortin** functions as well as valuable information for structure-based **drug** design involving the regulation of obesity and feeding.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L22 ANSWER 6 OF 17 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 128:240953 CA
TITLE: Interaction of Agouti protein with the **melanocortin** 1 receptor in vitro and in vivo
AUTHOR(S): Ollmann, Michael M.; Lamoreux, M. Lynn; Wilson, Brent D.; Barsh, Gregory S.
CORPORATE SOURCE: Departments of Pediatrics and Genetics, Stanford University School of Medicine, Stanford, CA, 94305-5428, USA
SOURCE: Genes Dev. (**1998**), 12(3), 316-330
CODEN: GEDEEP; ISSN: 0890-9369
PUBLISHER: Cold Spring Harbor Laboratory Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Agouti protein and Agouti-related protein (Agrp) are paracrine-signaling mols. that normally regulate pigmentation and body wt., resp. These proteins antagonize the effects of .alpha.-MSH (.alpha.-MSH) and other **melanocortins**, and several alternatives have been proposed to explain their biochem. mechanisms of action. We have used a sensitive bioassay based on Xenopus melanophores to characterize **pharmacol** . properties of recombinant Agouti protein, and have directly measured its cell-surface binding to mammalian cells by use of an epitope-tagged form (HA-Agouti) that retains biol. activity. In melanophores, Agouti protein has no effect in the absence of .alpha.-MSH, but its action cannot be explained solely by inhibition of .alpha.-MSH binding. In 293T cells, expression of the **Mc1r** confers a specific, high-affinity binding site for HA-Agouti. Binding is inhibited by .alpha.-MSH, or by Agrp, which indicates that .alpha.-MSH and Agouti protein bind in a mutually exclusive way to the **Mc1r**, and that the similarity between Agouti protein and Agrp includes their binding sites. The effects of Agouti and the **Mc1r** in vivo have been examd. in a sensitized background provided by the chinchilla (Tyrc-ch) mutation, which uncovers a phenotypic difference between overexpression of Agouti in lethal yellow (Ay/a) mice and loss of **Mc1r** function in recessive yellow (Mc1re/Mc1re) mice. Double and triple mutant studies indicate that a functional **Mc1r** is required for the pigmentary effects of Agouti, and suggest that Agouti protein can act as an agonist of the **Mc1r** in a way that differs from .alpha.-MSH stimulation. These results resolve questions regarding the biochem. mechanism of Agouti protein action, and provide evidence of a novel signaling mechanism whereby .alpha.-MSH and Agouti protein or Agrp function as independent ligands that inhibit each other's binding and transduce opposite signals through a single receptor.

L22 ANSWER 7 OF 17 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 128:226679 CA
TITLE: Methods and reagents for discovering and using mammalian **melanocortin** receptor agonists and antagonists to modulate feeding behavior in animals
INVENTOR(S): Cone, Roger D.; Fan, Wei; Boston, Bruce A.; Kesterton, Robert A.; Lu, Dongsi; Chen, Wenbiao
PATENT ASSIGNEE(S): Oregon Health Sciences University, USA; Cone, Roger D.; Fan, Wei; Boston, Bruce A.; Kesterton, Robert A.; Lu, Dongsi; Chen, Wenbiao
SOURCE: PCT Int. Appl., 122 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 6

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 9810068	A2	19980312	WO 1997-US15565	19970904	<--
WO 9810068	A3	19980625			
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
US 6100048	A	20000808	US 1996-706281	19960904	
AU 9741812	A1	19980326	AU 1997-41812	19970904	<--
AU 719954	B2	20000518			
EP 935655	A1	19990818	EP 1997-939799	19970904	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
JP 2001510984	T2	20010807	JP 1998-512888	19970904	

PRIORITY APPLN. INFO.:	US 1996-706281	A	19960904
	US 1992-866560	A3	19920410
	US 1992-886979	A3	19920410
	US 1993-44812	A2	19930408
	US 1995-466906	A2	19950606
	US 1995-478992	A2	19950607
	WO 1997-US15565	W	19970904

OTHER SOURCE(S): MARPAT 128:226679

AB The present invention provides recombinant expression constructs comprising nucleic acid encoding mammalian **melanocortin** receptors, and mammalian cells into which said recombinant expression constructs have been introduced that express functional mammalian **melanocortin** receptors. Thus, cDNAs for 7 different **melanocortin** receptors were cloned from mammalian sources: mouse and human .alpha.-MSH receptors, human and bovine ACTH receptors, rat **MC**-3 receptor, human **MC**-4 receptor, and mouse **MC**-5 receptor. The invention provides a panel of transformed mammalian cells expressing **melanocortin** receptors for screening compds. for receptor agonist and antagonist activity. The plasmid vector for the expression of the **melanocortin** receptors comprises the cAMP response element (CRE) linked to a reporter .beta.-galactosidase gene. The invention also provides methods for using such panels of **melanocortin** receptor-expressing mammalian cells to specifically detect and identify agonists and antagonists for each **melanocortin** receptor, as well as patterns of agonist and antagonist activity of said compds. for the class of **melanocortin** receptors. Such screening methods provide a means for identifying compds. with patterns of **melanocortin** agonist and antagonist activity which is assocd. with the capacity to influence or modify metab. and behavior, particularly feeding behavior.

L22 ANSWER 8 OF 17 CA COPYRIGHT 2002 ACS

ACCESSION NUMBER:	128:213520 CA
TITLE:	Characterization of the binding of MSH-B, HP-228, GHRP-6 and 153N-6 to the human **melanocortin** receptor subtypes
AUTHOR(S):	Schioth, H. B.; Muceniece, R.; Wikberg, J. E. S.
CORPORATE SOURCE:	Dep. Pharmaceutical Pharmacology, Uppsala Univ., Uppsala, Swed.

SOURCE: Neuropeptides (Edinburgh) (**1997**), 31(6), 565-571
CODEN: NRPPDD; ISSN: 0143-4179
PUBLISHER: Churchill Livingstone
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We detd. the binding affinities of the MSH analogs MSH-B, HP-228 and 153N-6 and of the enkephalin analog GHRP-6 on a single eukaryotic cell line transiently expressing the human MC1, MC3, MC4 and MC5 receptors. Moreover, we tested the binding and cAMP response of MSH-B in comparison with .alpha.-MSH on murine B16 melanoma cells. Our results indicate that MSH-B has a potency similar to that of .alpha.-MSH and that these two peptides induce similar cAMP responses in murine B16 melanoma cells. HP-228 has its highest affinity for the MC1 receptor. For the other receptors, it has slightly higher affinity for the MC5 receptor than for the MC3 and MC4 receptors. 153N-6 was found to be selective for the MC1 receptor. GHRP-6 was found to bind to the MC1 and the MC5 receptors despite its low structural homol. with .alpha.-MSH. [D-Lys3]GHRP-6 bound to all the four **MC** receptors with similar affinities. The structurally related Met-enkephalin and the functionally related GHRH, as well as LHRH and somatostatin-14 did not bind to these **MC** receptors. The low affinity of the GH-releasing/enkephalin peptides may indicate that they do not interact with the **MC** receptors at **pharmacol**. relevant concns.

L22 ANSWER 9 OF 17 CA

ACCESSION NUMBER: 127:117490 CA

TITLE: Dynorphin peptides: antagonists of **melanocortin** receptors

AUTHOR(S): Quillan, J. Mark; Sadee, Wolfgang
CORPORATE SOURCE: Departments of Biopharmaceutical Sciences and Pharmaceutical Chemistry, University of California Medical Center, San Francisco, CA, 94143-0446, USA

SOURCE: Pharm. Res. (**1997**), 14(6), 713-719
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Plenum
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To identify possible targets that mediate the non-opioid effects of dynorphin A (DynA), effects that include inflammation and aggravation of traumatic nerve injury. The authors examd. dynorphin peptides for functional interaction with the closely related **melanocortin** (**MC**) system. DynA-(1-13)NH2 and other related opioid dynorphin peptides antagonize the human MC1, MC3 and MC4 receptors, and an amphibian **MC** receptor, with dissocn. consts. (Kd's) of 40 to 150 nM. The affinity of dynorphin's interaction with **MC** receptors is therefore greater than with other previously proposed non-opioid targets of dynorphin, which require micromolar concns. Dynorphin also antagonizes the adrenocorticotropic hormone (ACTH; MC2) receptor and an **MC** -like receptor endogenous to COS-7 cells, but with lower efficacy. In contrast DynA had no effect on seven control receptors and was only weakly effective at two others. Metabolites of dynorphin derived from cleavage of the N-terminal Tyr residue, such as DynA(2-17), lack opioid activity yet still produce a no. of well established non-opioid effects. These des-Tyr derivs. also antagonized each of the five **MC** receptors examd. DynA peptides were found to antagonize **MC** receptors in vitro with potencies that parallel those reported for **pharmacol**. non-opioid effects of dynorphins in vivo. The combination of DynA and its active metabolites may reach levels sufficient to inhibit **MC** receptors physiol. Dynorphin inhibition of **MC** receptors could

prove to be an example of crosstalk between two distinct yet phylogenetically related neurotransmitter systems.

L22 ANSWER 10 OF 17 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 127:76042 CA
TITLE: **Melanocortins** and opiate addiction
AUTHOR(S): Alvaro, J. D.; Tatro, J. B.; Duman, R. S.
CORPORATE SOURCE: Lab. Molecular Psychiatry, Dep. Psychiatry Pharmacology, Yale Univ. School Medicine, New Haven, CT, 06511, USA
SOURCE: Life Sci. (**1997**), 61(1), 1-9
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 73 refs. Adrenocorticotropic hormone (ACTH) and .alpha.-MSH are centrally acting **melanocortin** peptides with numerous reported functions, including induction of excessive grooming and antipyresis, among others. Also reported is a role for **melanocortins** in aspects of opiate action. Although early work examd. the effects of ACTH and MSH on opiate-induced behaviors, further progress has been limited. Receptor (**MC**-R) subtypes have provided novel tools with which to study interactions between **melanocortins** and addiction. The present review discusses the effects of ACTH and MSH on opiate-induced behaviors and relates these findings to more recent reports on the regulation of **melanocortin** systems by exogenous opiates. Emerging from these data is the possibility that **melanocortin** receptor activation, specifically at the MC4-R subtype, may act to antagonize certain properties of exogenous opiates, including perhaps addiction.

L22 ANSWER 11 OF 17 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 126:166564 CA
TITLE: Three-dimensional molecular models of the hMC1R **melanocortin** receptor: complexes with melanotropin peptide agonists
AUTHOR(S): Haskell-Luevano, Carrie; Sawyer, Tomi K.; Trumpp-Kallmeyer, Susanne; Bikker, Jack A.; Humblet, Christine; Gantz, Ira; Hruby, Victor J.
CORPORATE SOURCE: Department of Chemistry, University of Arizona, Tucson, AZ, 85721, USA
SOURCE: Drug Des. Discovery (**1996**), 14(3), 197-211
CODEN: DDDIEV; ISSN: 1055-9612
PUBLISHER: Harwood
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Three-dimensional mol. models of the human **melanocortin** receptor (hMC1R) have been developed based upon the electron cryomicroscopic structure of bacteriorhodopsin and the electron d. footprint of bovine rhodopsin. .alpha.-MSH, Ac-Ser-Tyr-Ser-Met4-Glu-His-Phe7-Arg-Trp-Gly-Lys-Pro-Val-NH2 (.alpha.-MSH, .alpha.-melanotropin), and the superpotent, prolonged acting agonists, Ac-Ser-Tyr-Ser-Nle4-Glu-His-DPhe7-Arg-Trp-Gly-Lys-Pro-Val-NH2 (NDP-MSH) and Ac-Nle4-c[Asp5-His6-DPhe7-Arg8-Trp9-Lys10]-NH2 (MTII), have been modeled into the proposed binding sites with specific ligand-receptor interactions identified. The melanotropin sidechain **pharmacophores**, DPhe7 and Trp9, are proposed to interact with a hydrophobic network of receptor arom. residues in transmembrane regions 4, 5, 6, and 7. In addn., a hydrophilic network involving the ligand Arg8 and polar receptor residues located in transmembrane regions 2 and 3 were identified. Biol. studies on

.alpha.-MSH, NDP-MSH, MTII, and related peptides have been correlated with the proposed hMC1R model in terms of agonism, affinity, and prolongation. Finally, limited **MC1R** mutagenesis studies comparing .alpha.-MSH and NDP-MSH are interpreted within the context of the proposed hMC1R models.

L22 ANSWER 12 OF 17 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 125:159005 CA
TITLE: Major **pharmacological** distinction of the ACTH receptor from other **melanocortin** receptors
AUTHOR(S): Schioeth, Helgi B.; Chhajlani, Vijay; Muceniece, Ruta; Klusa, Vija; Wikberg, Jarl E. S.
CORPORATE SOURCE: Dep. Pharmaceutical Pharmacol., Uppsala Univ., Uppsala, Swed.
SOURCE: Life Sci. (**1996**), 59(10), 797-801
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mouse adrenocortical cell line Y1, that expresses ACTH receptors (**MC2R**), was used to probe the binding of ACTH and MSH peptides by using radio-labeled ACTH (1-39). The Y1 cells were found to bind [125I]-labeled ACTH(1-39) with high affinity (Kd.apprx.130 pM). However, none of the **melanocortin** peptides NDP-MSH, .alpha.-MSH, .beta.-MSH or .gamma.1-MSH could compete with the binding of the labeled ACTH(1-39). When other **MC** receptor subtype DNAs (MC1, MC3 and MC4) were transfected into the Y1 cells, characteristic binding of the [125]NDP-MSH appeared for each of the receptor subtype, but no specific binding was present in non-transfected cells. This is the first report clearly demonstrating that the ACTH receptor binds only ACTH, but not other **melanocortin** peptides.

L22 ANSWER 13 OF 17 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 123:219291 CA
TITLE: **Melanocortin** receptors 5 and the genes encoding them and their **pharmacological** use
INVENTOR(S): Griffon, Nathalie; Sokoloff, Pierre; Mignon, Virginie; Diaz, Jorge; Facchinetti, Patricia; Schwartz, Jean-Charles
PATENT ASSIGNEE(S): Institut National de la Sante et de la Recherche Medicale (INSERM), Fr.
SOURCE: Fr. Demande, 39 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2713645	A1	19950616	FR 1993-14732	19931208 <--

AB Proteins that act as receptors for **melanocortins**, particularly ACTH and MSH and the genes encoding them are identified for use in the screening of potential therapeutic agents acting on the receptor (no data). Specifically, a novel receptor, **MC**-5, is identified. The rat gene was cloned as a sequence cross-hybridizing with a probe derived from the D3 dopaminergic receptor gene. A partial sequence from this clone indicated a strong similarity to other **melanocortin** receptors. The rat clone was used to screen a human library. The rat gene was expressed in CHO cells using a com. expression vector and a

receptor that responded most strongly to 1-24-ACTH and .alpha.-MSH was presented by the cells. This **pharmacol**. is distinct from that of other **melanocortin** receptors. The rat gene was strongly expressed in the stomach and adrenal.

L22 ANSWER 14 OF 17 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 121:293188 CA
TITLE: Localization of the **melanocortin**-4 receptor (MC4-R) in neuroendocrine and autonomic control circuits in the brain
AUTHOR(S): Mountjoy, Kathleen G.; Mortrud, Marty T.; Low, Malcolm J.; Simerly, Richard B.; Cone, Roger D.
CORPORATE SOURCE: Vollum Inst. for Advanced Biomedical Research, Oregon Health Sciences Univ., Portland, OR, 97201-3098, USA
SOURCE: Mol. Endocrinol. (**1994**), 8(10), 1298-308
CODEN: MOENEN; ISSN: 0888-8809
DOCUMENT TYPE: Journal
LANGUAGE: English
AB POMC, the precursor of ACTH, MSH, and .beta.-endorphin peptides, is expressed in the pituitary and in two sites in the brain, in the arcuate nucleus of the hypothalamus and the commissural nucleus of the solitary tract of the brain stem. Little is known regarding the functions of **melanocortin** (ACTH and MSH) peptides in the brain. The authors report here the detailed neuroanatomical distribution of the MC4-R mRNA in the adult rat brain. The **melanocortin** 3 receptor (MC3-R), characterized previously, was found to be expressed in arcuate nucleus neurons and in a subset of their presumptive terminal fields but in few regions of the brainstem. The highly conserved MC4-R is much more widely expressed than MC3-R and is **pharmacol**. distinct. MC4-R mRNA was found in multiple sites in virtually every brain region, including the cortex, thalamus, hypothalamus, brainstem, and spinal cord. Unlike the MC3-R, MC4-R mRNA is found in both parvicellular and magnocellular neurons of the paraventricular nucleus of the hypothalamus, suggesting a role in the central control of pituitary function. MC4-R is also unique in its expression in numerous cortical and brainstem nuclei. Together, MC3-R and/or **MC-4R** mRNA are found in every nucleus reported to bind MSH in the adult rat brain and define neuronal circuitry known to be involved in the control of diverse neuroendocrine and autonomic functions. The high degree of conservation, distinct **pharmacol** ., and unique neuronal distribution of the MC4 receptor suggest specific and complex roles for the **melanocortin** peptides in neuroendocrine and autonomic control.

L22 ANSWER 15 OF 17 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 121:74078 CA
TITLE: Molecular cloning, expression, and characterization of a fifth **melanocortin** receptor
AUTHOR(S): Gantz, Ira; Shimoto, Yoshimasa; Konda, Yoshitaka; Miwa, Hiroto; Dickinson, Chris J.; Yamada, Tadataka
CORPORATE SOURCE: Dep. Surg., Univ. Michigan Med. Cent., Ann Arbor, MI, USA
SOURCE: Biochem. Biophys. Res. Commun. (**1994**), 200(3), 1214-20
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors report the isolation of a gene encoding a novel member of the family of **melanocortin** receptors. The mouse **melanocortin**-5 receptor (mMC5R) responds to **melanocortins** with an increase in intracellular cyclic 3',5'-adenosine monophosphate

(cAMP) concns. Stimulation of the mMC5R by the **melanocortins** revealed a hierarchy of potency in which .alpha.-MSH (.alpha.-MSHZ) >.beta.-MSH (.beta.-MSH) >adrenocorticotropic hormone (ACTH) >.gamma.-MSH (.gamma.-MSH). Further structure-activity studies indicated that amino- and carboxyl-terminal portions of .alpha.-MSH appear to be key determinants in the activation of mMC5R whereas the **melanocortin** core heptapeptide sequence is devoid of **pharmacol**. activity. Northern blot anal. demonstrated the expression of mMC5R mRNA in mouse skeletal muscle, lung, spleen, and brain.

L22 ANSWER 16 OF 17 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 121:50841 CA
TITLE: Human melanocyte stimulating hormone receptors and cDNAs encoding them
INVENTOR(S): Wikberg, Jarl; Chhajlani, Vijay
PATENT ASSIGNEE(S): Swed.
SOURCE: PCT Int. Appl., 138 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 9404674	A1	19940303	WO 1993-DK273	19930820	<--
W: AU, BB, BG, BR, BY, CA, CZ, FI, HU, JP, KP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, US, VN					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
EP 656944	A1	19950614	EP 1993-917583	19930820	<--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
JP 08502883	T2	19960402	JP 1993-505795	19930820	<--
AU 691472	B2	19980521	AU 1993-46997	19930820	<--
EP 1160322	A2	20011205	EP 2001-110664	19930820	
EP 1160322	A3	20020102			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE					
FI 9500784	A	19950321	FI 1995-784	19950221	<--

PRIORITY APPLN. INFO.:

DK 1992-1046	A	19920821
DK 1992-1118	A	19920910
DK 1993-528	A	19930505
EP 1993-917583	A3	19930820
WO 1993-DK273	W	19930820

AB Novel cDNAs encoding melanotropic hormone receptors, esp. MSH receptors, and the proteins they encode are described for use in the prepn. of the protein and monoclonal antibodies for diagnostic and therapeutic purposes and in the design of **drugs** (no data). Methods for treatment and diagnosis of malignant melanoma, skin cancer, vitiligo, pyretic conditions, inflammatory disease, pain, catatonia, impaired memory, reduced or increased skin tanning, pigmentation condition, epilepsy and nerve damage, using the DNA fragments, polypeptides and antibodies are described. Methods for selecting substances which interact with the receptors are also disclosed. Primers derived from the conserved transmembrane domains of G protein coupled receptors were used to amplify human genomic DNA and three amplification products were found; one of these was novel and investigated further. The gene from which this fragment was derived was strongly expressed in melanoma cells (WM266-4) and a random primed cDNA bank from this line was screened and a pos. clone obtained. Expression of the cDNA in COS-7 resulted in the appearance of a receptor with the MSH analog-binding properties of the MSH receptor. Two

related cDNAs were cloned.

L22 ANSWER 17 OF 17 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 121:50366 CA
TITLE: Cloning and expression of a new member of the melanocyte-stimulating hormone receptor family
AUTHOR(S): Barrettt, P.; MacDonald, A.; Helliwell, R.; Davidson, G.; Morgan, P.
CORPORATE SOURCE: Mol. Neuroendocrinol. Group, Rowett Res. Inst., Bucksburn/Aberdeen, AB2 9SB, UK
SOURCE: J. Mol. Endocrinol. (**1994**), 12(2), 203-13
CODEN: JMLEEI; ISSN: 0952-5041
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A new member of the G protein-coupled receptor superfamily has been isolated from an ovine genomic library with a probe generated by the application of the PCR technique, using cDNA synthesized on a mRNA template isolated from the ovine pars tuberalis. This genomic clone encodes a novel receptor of 325 amino acids with seven transmembrane domains. These domains share homol. with other members of this family, but the best homol. is with the recently cloned human **MC**-1 (50% in the transmembrane domains) and **MC**-3 (69% in the transmembrane domains) MSH receptors and the human ACTH (42% in the transmembrane domains) receptor. When this receptor was expressed in Cos7 cells, it was able to bind a potent analog of .alpha.-MSH, [Nle4,D-Phe7]-.alpha.-MSH (NDP-MSH), with high affinity. This binding could be displaced by pro-opiomelanocortin-derived and related peptides, with the order of potency NDP-MSH > .alpha.-MSH = ACTH > .beta.-MSH and with no effect on .gamma.-MSH, .delta.-MSH or .beta.-endorphin. The expressed receptor was demonstrated to be functionally coupled to the adenylate cyclase second messenger pathway, with .alpha.-MSH, .beta.-MSH and ACTH stimulating cAMP prodn. The amt. of the mRNA for this receptor was found to be very low. The tissue distribution of this receptor could only be obsd. using the reverse transcription-PCR technique and the receptor was found to be present in a no. of somatic tissues. These data indicate that this is a new and distinct member of the **melanocortin** receptor family.

=> D IBIB ABS 1-50

L23 ANSWER 1 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 132:289224 CA
TITLE: **Melanocortin** receptor antagonists and agonists
INVENTOR(S): Huby, Victor J.; Lim, Sejin; Yuan, Wei
PATENT ASSIGNEE(S): The Arizona Board of Regents on Behalf of the University of Arizona, USA
SOURCE: U.S., 10 pp., Cont.-in-part of U.S. 5,731,408.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6054556	A	20000425	US 1997-980238	19971128
US 5731408	A	19980324	US 1995-420972	19950410 <--

PRIORITY APPLN. INFO.: US 1995-420972 19950410
AB Cyclic lactam heptapeptides (which are **melanocortin** analogs) are

disclosed which inhibit at various levels of antagonism the **melanocortin** 1 receptor (**MC1R**), **melanocortin** 3 receptor (**MC3R**), **melanocortin** 4 receptor (**MC4R**), and **Melanocortin** 5 receptor (**MC5R**).
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 2 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 131:28503 CA
TITLE: Evolutionarily conserved telomeric location of BBC1 and **MC1R** on a microchromosome questions the identity of **MC1R** and a pigmentation locus on chromosome 1 in chicken
AUTHOR(S): Sazanov, Alexei; Masabanda, Julio; Ewald, Dagmar; Takeuchi, Sakae; Tixier-Boichard, Michele; Buitkamp, Johannes; Fries, Ruedi
CORPORATE SOURCE: Lehrstuhl fur Tierzucht der Technischen Universitat, Freising-Weihenstephan, 85350, Germany
SOURCE: Chromosome Res. (**1998**), 6(8), 651-654
CODEN: CRRSEE; ISSN: 0967-3849
PUBLISHER: Rapid Science Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **MC1R** (**melanocortin**-1 receptor gene) and BBC1 (breast basic conserved gene 1) are closely linked in human chromosome 16q24.3. Fluorescence in situ hybridization (FISH) with the cosmids specific for **MC1R** and BBC1 was performed. In all metaphases analyzed, distinct signals were obsd. at the telomeric region of a microchromosome in size range of GGA15 to GGA20. The two loci are not only closely linked in humans and in chicken but also located in a telomeric band in both species. A locus controlling the relative amts. of eumelanin/phaeomelanin was tentatively mapped to GGA1. However, the evolutionarily conserved location of **MC1R** on a chicken microchromo- some and the possibility of variants in **MC1R** being responsible for E-specific alleles introduce an apparent contradiction between phys. mapping data and genetic mapping data and raise some doubt about the identity of the E locus and **MC1R** in chicken.
REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 3 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:262371 CA
TITLE: Expression of ACTH receptors (MC2-R and MC5-R) in the glomerulosa and the fasciculata-reticularis zones of bovine adrenal cortex
AUTHOR(S): Liakos, P.; Chambaz, E. M.; Feige, J. J.; Defaye, G.
CORPORATE SOURCE: CEA, INSERM U. 244, DBMS, Grenoble, 38054, Fr.
SOURCE: Endocr. Res. (**1998**), 24(3 & 4), 427-432
CODEN: ENRSE8; ISSN: 0743-5800
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The recent cloning of a family of **melanocortin** receptors (**MC**-R) has identified five distinct G protein- and adenylate cyclase-coupled receptors. The MC2-receptor (MC2-R) preferentially binds ACTH. It is expressed in the adrenal cortex and is hence considered to be the ACTH receptor. The MC5-receptor (MC5-R) binds ACTH and .alpha.-MSH and is more widely expressed. The aim of this work was to study the sites of MC5-R expression in the bovine adrenal cortex and to compare the regulation of the expression of MC2-R and MC5-R in bovine adrenocortical

cells in primary culture. Anal. of the expression of MC5-R was obtained by RT-PCR, using total RNA purified from glomerulosa and fasciculata zones of bovine adrenocortical tissue. MC5-R expression could be detected in RNA from the glomerulosa zone but was undetectable in the fasciculata zone. In bovine adrenocortical cells in culture, ACTH stimulates MC5-R expression in the glomerulosa and fasciculata cells. A DNA fragment, was obtained using primers based on the bovine ACTH receptor (MC2-R) sequence. This fragment was detected in RNA from the two zones. The probe was used to quantify MC2-R by RNase Protection assay and the authors obsd. that MC2-R mRNA is 3.6-fold more abundant in glomerulosa than in fasciculata-reticularis cells.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 4 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:177673 CA
TITLE: Amino acid residues in third intracellular loop of **melanocortin** 1 receptor are involved in G-protein coupling
AUTHOR(S): Frandberg, Per-Anders; Doufexis, Marina; Kapas, Supriya; Chhajlani, Vijay
CORPORATE SOURCE: Division of Biological Research on Drug Dependence, Biomedical Centre, Uppsala, S-751 24, Swed.
SOURCE: Biochem. Mol. Biol. Int. (**1998**), 46(5), 913-922
CODEN: BMBIES; ISSN: 1039-9712
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To delineate domains essential for G-protein coupling in **melanocortin** 1 receptor (**MC1R**), we mutated polar and basic residues to alanine at eleven positions in the putative third intracellular loop and detd. consequent changes in the ligand binding and generation of second messenger cAMP. Results demonstrate that ligand binding affinity was not affected by any of the mutations. However, every mutant displayed reduced functional response as compared to the wild type receptor. Replacement of residues (K226, R227, Q228, R229, H232, Q233 and K238) present in the 2nd half of the 3rd intracellular loop resulted in an almost complete loss of functional response. The results demonstrated that the amino acid residues in the 3rd intracellular loop are involved in coupling to G-protein and that a region of 4 amino acids, K226-R227-Q228-R229, is essential for coupling of **MC1R** to G-protein. (c) 1998 Academic Press.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 5 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:166912 CA
TITLE: HLA-independent heterogeneity of CD8+ T cell responses to MAGE-3, melan-A/MART-1, gp100, tyrosinase, **MC1R**, and TRP-2 in vaccine-treated melanoma patients
AUTHOR(S): Reynolds, Sandra R.; Celis, Esteban; Sette, Alessandro; Oratz, Ruth; Shapiro, Richard L.; Johnston, Dean; Fotino, Marilena; Bystryn, Jean-Claude
CORPORATE SOURCE: Ronald O. Perelman Dep. Dermatol., New York Univ. Med. Cent., New York, NY, 10016, USA
SOURCE: J. Immunol. (**1998**), 161(12), 6970-6976
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists

DOCUMENT TYPE: Journal
LANGUAGE: English
AB An important element in melanoma vaccine construction is to identify peptides from, melanoma-assocd. Ags that have immunogenic potential in humans and are recognized by CD8+ T cells in vivo. To identify such peptides, the authors evaluated HLA-A*02+ melanoma patients immunized to a polyvalent vaccine contg. multiple Ags, including MAGE-3, Melan-A/MART-1, gp100, tyrosinase, **melanocortin** receptor (**MC1R**), and dopachrome tautomerase (TRP-2). Using a filter spot assay, the authors measured peripheral blood CD8+ T cell responses, before and after immunization, to a panel of 45 HLA-A*0201-restricted peptides derived from these Ags. The peptides were selected for immunogenic potential based on their strong binding affinity in vitro to HLA-A*0201. Vaccine treatment induced peptide-specific CD8+ T cell responses to 22 (47.8%) of the peptides. The most striking finding was the HLA-independent heterogeneity of responses to both peptides and Ags. All responding patients reacted to different combination of peptides and Ags even though the responding patients were all A*0201+ and the peptides were all A*0201-restricted. From 9 to 27% of patients developed a CD8+ T cell response to at least one peptide from each Ag, but no more than 3 (14%) reacted to same peptide from the same Ag. This heterogeneity of responses to individual peptides and Ags in patients with the same haplotype points to the need to construct vaccines of multiple peptides or Ags to maximize the proportion of responding patients.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 6 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:148812 CA
TITLE: **Melanocortin** receptor 1 (**MC1R**) mutations and coat color in pigs
AUTHOR(S): Kijas, J. M. H.; Wales, R.; Tornsten, A.; Chardon, P.; Moller, M.; Andersson, L.
CORPORATE SOURCE: Department of Animal Breeding and Genetics, Swedish University of Agricultural Sciences, Uppsala, S-751 24, Swed.
SOURCE: Genetics (**1998**), 150(3), 1177-1185
CODEN: GENTAE; ISSN: 0016-6731
PUBLISHER: Genetics Society of America
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The **melanocortin** receptor 1 (**MC1R**) plays a central role in regulation of eumelanin (black/brown) and phaeomelanin (red/yellow) synthesis within the mammalian melanocyte and is encoded by the classical Extension (E) coat color locus. Sequence anal. of **MC1R** from seven porcine breeds revealed a total of four allelic variants corresponding to five different E alleles. The European wild boar possessed a unique **MC1R** allele that the authors believe is required for the expression of a wild-type coat color. Two different **MC1R** alleles were assocd. with the dominant black color in pigs. **MC1R***2 was found in European Large Black and Chinese Meishan pigs and exhibited two missense mutations compared with the wild-type sequence. Comparative data strongly suggest that one of these, L99P, may form a constitutively active receptor. **MC1R***3 was assocd. with the black color in the Hampshire breed and involved a single missense mutation D121N. This same **MC1R** variant was also assocd. with Ep, which results in black spots on a white or red background. Two different missense mutations were identified in recessive red (e/e) animals. One of these, A240T, occurs at a highly conserved position, making it a strong candidate for disruption of receptor function.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 7 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:134078 CA
TITLE: Discovery of a novel superpotent and selective **melanocortin**-4 receptor antagonist (HS024): evaluation in vitro and in vivo
AUTHOR(S): Kask, Ants; Mutulis, Felikss; Muceniece, Ruta; Pahkla, Rein; Mutule, Ilze; Wikberg, Jarl E. S.; Rago, Lembit; Schioth, Helgi B.
CORPORATE SOURCE: Department of Pharmacology, University of Tartu, Tartu, 50090, Estonia
SOURCE: Endocrinology (**1998**), 139(12), 5006-5014
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Several novel cyclic MSH analogs were synthesized, and their binding properties were tested on cells transiently expressing the human **melanocortin**-1 (MC1), MC3, MC4, and MC5 receptors. We discovered a novel substance (HS024) that showed about 20-fold selectivity and very high affinity (Ki = 0.29 nM) for the MC4 receptor. HS024 (cyclic [AcCys3,Nle4,Arg5,D-Nal7,Cys-NH211].alpha.-MSH-(3-11)) has a 29-membered atom ring structure that includes an Arg in position 5. HS024 was found to antagonize an .alpha.MSH-induced cAMP response in cells expressing the human MC1, MC3, MC4, and MC5 receptor DNAs. HS024 also caused a dose-dependent increase in food intake, with a max. response (4-fold increase) at a 1-nmol dose injected intracerebroventricularly in free feeding rats. We also tested SHU9119, a previously described nonselective **MC** receptor antagonist, and found HS024 and SHU9119 to have similar potencies for increasing food intake, although SHU9119 appeared to induce more serious side-effects. HS024 increased the food intake of free feeding rats to levels comparable to those in food-deprived rats, indicating that blockade of the MC4 receptor is a highly effective way to increase feeding. Moreover, we tested the effects of intracerebroventricular injections of HS024 in elevated plus-maze and open-field expts. on rats. In these tests, HS024 did not appear to affect emotionality or locomotor activity, suggesting that the MC4 receptor does not mediate the anxiogenic-like and locomotor effects related to the melanocortic peptides.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 8 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:105877 CA
TITLE: Assignment of the **melanocortin** 4 receptor (**MC4R**) gene to human chromosome band 18q22 by in situ hybridization and radiation hybrid mapping
AUTHOR(S): Sundaramurthy, D.; Campbell, D. A.; Leek, J. P.; Markham, A. F.; Pieri, L. F.
CORPORATE SOURCE: Molecular Medicine Unit, University of Leeds, St James's University Hospital, Leeds, UK
SOURCE: Cytogenet. Cell Genet. (**1998**), 82(1-2), 97-98
CODEN: CGCGBR; ISSN: 0301-0171
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this report radiation hybrid panel mapping and fluorescence in situ

hybridization (FISH) were used to reassign the human **melanocortin** -4 receptor (**MC4R**) gene more telomerically at chromosome band 18q22. This FISH data indicates that the human **MC4R** gene is more distal to the previously established location (Gantz et al., 1993b, Gerken et al., 1994). Our data support the findings of Magenis et al. (1994) who also mapped the gene to 18q22. For the radiation hybrid panel, **MC4R** was positioned on the human chromosome 18 framework map 3.25 cR3000 below WI-4461.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 9 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:105500 CA
TITLE: Brainstem application of **melanocortin** receptor ligands produces long-lasting effects on feeding and body weight
AUTHOR(S): Grill, Harvey J.; Ginsberg, Abigail B.; Seeley, Randy J.; Kaplan, Joel M.
CORPORATE SOURCE: Department of Psychology and Institute of Neurological Sciences, University of Pennsylvania, Philadelphia, PA, 19104, USA
SOURCE: J. Neurosci. (**1998**), 18(23), 10128-10135
CODEN: JNRSDS; ISSN: 0270-6474
PUBLISHER: Society for Neuroscience
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent evidence suggests that the central **melanocortin** (**MC**) system is a prominent contributor to food intake and body wt. control. **MC** receptor (**MC**-R) populations in the arcuate and paraventricular nuclei are considered probable sites of action mediating the orexigenic effects of systemically or intracerebroventricularly administered ligands. Yet, the highest MC4-R d. in the brain is found in the dorsal motor nucleus of the vagus nerve, situated subjacent to the commissural nucleus of the solitary tract, a site of pro-opiomelanocortin mRNA expression. We evaluated the contribution of the caudal brainstem **MC** system by (1) performing resp. dose-response analyses for an **MC**-R agonist (MTII) and antagonist (SHU 9119) delivered to the fourth ventricle, (2) comparing, in the same rats, the fourth intracerebroventricular dose-response profiles to those obtained with lateral intracerebroventricular delivery, and (3) delivering an ED of MTII or SHU 9119 to rats before a 24 h period of food deprivation. Fourth intracerebroventricular agonist treatment yielded a dose-dependent redn. of short-term (2 and 4 h) and longer-term (24 h) food intake and body wt. Fourth intracerebroventricular antagonist treatment produced the opposite pattern of results: dose-related increases in food intake and corresponding increases in body wt. change for the 24-96 h observation period. Comparable dose-response functions for food intake and body wt. were obsd. when these compds. were delivered to the lateral ventricle. Results from deprived rats (no effect of MTII or SHU 9119 on wt. loss) support the impression derived from the dose-response analyses that the body wt. change that follows **MC** treatments is secondary to their resp. effects on food intake. Results support the relevance of the brainstem **MC**-R complement to the control of feeding.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 10 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:90608 CA
TITLE: Autoradiographic discrimination of **melanocortin** receptors indicates that the MC3

subtype dominates in the medial rat brain
AUTHOR(S): Lindblom, Jonas; Schioth, Helgi B.; Larsson, Anna; Wikberg, Jarl E. S.; Bergstrom, Lena
CORPORATE SOURCE: BMC, Box 591, Division of Pharmacology, Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, S-751 24, Swed.
SOURCE: Brain Res. (**1998**), 810(1,2), 161-171
CODEN: BRREAP; ISSN: 0006-8993
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In the present study, we developed an autoradiog. method to visualize the distribution of **melanocortin** (**MC**) receptors 3 and 4 in sagittal sections of the rat brain. The method takes advantage of the MC3 and MC4 receptor selective compds., .gamma.1-MSH and HS 014. First, we characterized the binding of .gamma.1-MSH, HS 014 and the radioligand [125I]NDP-MSH to the rat MC3 and MC4 receptors expressed in COS cells. [125I]NDP-MSH was found to be non-selective, whereas .gamma.1-MSH showed a 40-fold preference for the rat MC3 receptor, and HS 014 an over 300-fold preference to the rat MC4 receptor. Second, to discriminate between the MC3 and MC4 receptors in rat brain sections, the sections were incubated with [125I]NDP-MSH in the presence of graded concns. of the MC3 selective ligand, .gamma.1-MSH, or the MC4 selective ligand, HS 014. From the autoradiograms thus made, competition curves of .gamma.1-MSH and HS 014 could be constructed for different regions of the rat brain. Our results indicate that in the nucleus accumbens shell, the medial preoptic area, and the ventromedial nucleus of the hypothalamus, there is a clear dominance of the MC3 receptor, whereas in the lateral septum and the olfactory tubercle, there seem to be present both MC3 and MC4 receptors, although the MC3 receptor may still be the dominating subtype. In the optic layer of the superior colliculus, our data indicate a more abundant expression of the MC4 receptor. In the ventral tegmental area, there might be an addnl. MSH-peptide binding site of unknown origin.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 11 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:78831 CA
TITLE: **Melanocortin** receptor genes in the chicken-tissue distributions
AUTHOR(S): Takeuchi, Sakae; Takahashi, Sumio
CORPORATE SOURCE: Department of Biology, Faculty of Science, Okayama University, Okayama, 700-8530, Japan
SOURCE: Gen. Comp. Endocrinol. (**1998**), 112(2), 220-231
CODEN: GCENA5; ISSN: 0016-6480
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two receptor genes belonging to the **melanocortin** receptor (**MC**-R) family were isolated in the chicken, the CMC4 and CMC5, each of which is a chicken homolog of the mammalian MC4-R and MC5-R, resp. The CMC4 encodes a 331 amino acid protein, sharing 86.4-88.1% identity with mammalian analogs, and the CMC5 encodes a 325 amino acid protein, which is 72.3-79.1% identical to mammalian counterparts. Both genes contain no intron in their coding regions and exist in the chicken genome as single copy genes. Reverse transcription-PCR anal. revealed that the CMC4 mRNA is expressed in a wide variety of peripheral tissues, including the adrenal, gonads, spleen, and adipose tissues, as well as in the brain, where mammalian counterparts are exclusively expressed in the brain,

indicating that the regulation of MC4-R gene expression differs between mammals and chickens. The CMC5 mRNA, on the other hand, is expressed in the liver, gonads, adrenal, kidney, brain, and adipose tissues as well as in the uropygial gland. These findings raise the possibility that **melanocortins** affect a variety of functions both in the brain and in the peripheral tissues of the chicken. (c) 1998 Academic Press.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 12 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:33437 CA
TITLE: Response of neuropeptide Y-deficient mice to feeding effectors
AUTHOR(S): Hollopeter, Gunther; Erickson, Jay C.; Seeley, Randy J.; Marsh, Donald J.; Palmiter, Richard D.
CORPORATE SOURCE: Howard Hughes Medical Institute and Department of Biochemistry, University of Washington, Seattle, WA, 98195, USA
SOURCE: Regul. Pept. (**1998**), 75-76, 383-389
CODEN: REPPDY; ISSN: 0167-0115
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Neuropeptide Y (NPY) is thought to be an important central regulator of feeding behavior and body wt. However, mice lacking NPY due to targeted genetic deletion do not display abnormalities in food intake or body wt. with ad libitum access to food or in response to fasting. In this study, we investigate the response of NPY-deficient (NPY-/-) mice to anorexic and orexigenic treatments. The dose-dependent stimulation of food intake by central NPY administration was unaltered in NPY-/- mice. Peripheral administration of various doses of leptin for 2 days elicited a two-fold greater inhibition of food intake in NPY-/- mice than in wild-type (NPY+/+) mice. In addn., lateral ventricular administration of leptin (1 .mu.g) suppressed refeeding in NPY-/- mice after a 24 h fast, but had little effect in NPY+/+ mice. However, the response to other feeding inhibitors such as ACTH-releasing factor (CRF), dexfenfluramine, and a **melanocortin** 4 receptor (**MC4R**) agonist, MTII, was unaltered in NPY-/- mice. These results indicate that the appetite-suppressant action of exogenous leptin is uniquely amplified in NPY-/- mice, and suggest that NPY may tonically antagonize leptin action.
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 13 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:23745 CA
TITLE: A frameshift mutation in human **MC4R** is associated with a dominant form of obesity
AUTHOR(S): Vaisse, Christian; Clement, Karine; Guy-Grand, Bernard; Froguel, Philippe
CORPORATE SOURCE: Inst. Biol.-CNRS EP10, Inst. Pasteur Lille Calmette, Lille, 59000, Fr.
SOURCE: Nat. Genet. (**1998**), 20(2), 113-114
CODEN: NGENEC; ISSN: 1061-4036
PUBLISHER: Nature America
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The presence of a heterozygous frameshift mutation resulting from a 4-bp insertion at nucleotide 732 of the coding sequence was found in gene **MC4R** of an obese patient. This insertion would result in the expression of a nonfunctional truncated **melanocortin**-4 receptor

lacking the 6th and 7th transmembrane domains, the latter of which would be replaced by a short abnormal C-terminal domain. The data indicate that a mutation in **MC4R** can cause a non-syndromic form of obesity with a monogenic dominant form of inheritance in humans.

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 14 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:23744 CA
TITLE: A frameshift mutation in **MC4R** associated with dominantly inherited human obesity
AUTHOR(S): Yeo, Giles S. H.; Farooqi, Sadaf; Aminian, Shiva; Halsall, David J.; Stanhope, Richard G.; O'Rahilly, Stephen
CORPORATE SOURCE: University Departments of Med. and Clinical Biochem., Addenbrooke's Hospital, Cambridge, UK
SOURCE: Nat. Genet. (**1998**), 20(2), 111-112
CODEN: NGENEC; ISSN: 1061-4036
PUBLISHER: Nature America
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A cohort of 63 severely obese children with no known cause for the obesity were screened for mutations in their **melanocortin**-4 receptor gene (**MC4R**). One 4-yr-old subject was identified who is heterozygous for a 4-bp deletion at codon 211. This results in a frameshift that introduces 5 aberrant amino acids culminating a stop codon in the region encoding the 5th transmembrane domain, resulting in a truncated protein. This mutation is likely to result in a nonfunctional receptor.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 15 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 130:4051 CA
TITLE: Design of potent and specific melanotropin agonists and antagonists: investigating ligands for new receptors
AUTHOR(S): Hruby, V. J.; Sharma, S. D.; Lim, S.; Yuan, W.; Haskell-Luevano, C.; Han, G.; Hadley, M. E.; Cone, R. D.; Gantz, I.
CORPORATE SOURCE: Department of Chemistry, University of Arizona, Tucson, AZ, 85721, USA
SOURCE: Pept. 1996, Proc. Eur. Pept. Symp., 24th (**1998**), Meeting Date 1996, 485-486. Editor(s): Ramage, Robert; Epton, Roger. Mayflower Scientific: Kingswinford, UK.
CODEN: 66RCA5
DOCUMENT TYPE: Conference
LANGUAGE: English

AB .alpha.-Melanotropin (.alpha.-MSH, Ac-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH2) analogs were synthesized by solid phase methods and bioactivities at the **melanocortin** hMC3 and hMC4 receptors detd. by bioassays which examd. cAMP stimulation directly or through a coupled assay. They provided excellent leads toward potent and selective agonists and antagonists at the MC3 and MC4 receptors and their structure-activity relationships were described. For example, when a bulky arom. .alpha.-amino acid is placed at position 7 of the cyclic 4 to 10 lactam analogs of .alpha.-MSH (4-10) such as Ac-Nle4-c[Asp5,D-Nal(pI)7, Lys10].alpha.-MSH (I) and Ac-Nle4-c[Asp5,D-Nal(2')7, Lys10].alpha.-MSH (II) potent antagonists at the classical frog skin **MC1R** and the hMC3R and hMC4R with selectivity for the MC4 receptor were obtained.

Interestingly, I and II were potent agonists at the hMC1R. However, a bulky substituent at position 7, or with D-Nal(2') with Nle8 (instead of Arg8) led resp. to agonist Ac-Nle4-c[Asp5,Nal(2')7,Lys10].alpha.-MSH(4-10)-NH2 which was selective for the hMC4R (20 to 200 fold), and Ac-Nle4-c[Asp5,D-Nal(2')7,Nle8, Lys10].alpha.-MSH(4-10)-NH2 which was selective fro the hMC1R (100 to 1,000 fold).

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L23 ANSWER 16 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 129:276282 CA
TITLE: Design and bioactivities of melanotropic peptide agonists and antagonists: design based on a conformationally constrained somatostatin template
AUTHOR(S): Hruby, Victor J.; Han, Guoxia; Hadley, Mac E.
CORPORATE SOURCE: Department of Chemistry, University of Arizona, Tucson, AZ, 85721, USA
SOURCE: Lett. Pept. Sci. (**1998**), 5(2-3), 117-120
CODEN: LPSCEM; ISSN: 0929-5666
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB .alpha.-Melanotropin and ACTH, POMC peptides, initiate biol. activity by interaction with the classical pigment cell (.alpha.-MSH receptor, **MC1R**) and adrenal gland (ACTH receptor, **MC2R**) **melanocortin** receptors, resp. The recently discovered **MC3R**, **MC4R** and **MC5R** receptors provide new targets and new biol. functions for POMC peptides. We have developed conformationally constrained .alpha.-melanotropin peptides that interact with all of these receptors as agonists and antagonists and are examg. new approaches to obtain highly selective ligands for each of these **melanocortin** receptors. Previously, we had converted somatostatin-derived peptides into potent and highly selective analogs that act as antagonists at the .mu. opioid receptors. Using the reverse turn template that came out of these studies, we have designed, de novo, agonist and antagonist peptide analogs that interact with **melanocortin** receptors.

L23 ANSWER 17 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 129:228754 CA
TITLE: Evidence that orexigenic effects of **melanocortin** 4 receptor antagonist HS014 are mediated by neuropeptide Y
AUTHOR(S): Kask, Ants; Rago, Lembit; Korrovits, Paul; Wikberg, Jarl E. S.; Schioth, Helgi B.
CORPORATE SOURCE: Department of Pharmacology, University of Tartu, Tartu, EE-2400, Estonia
SOURCE: Biochem. Biophys. Res. Commun. (**1998**), 248(2), 245-249
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent studies using **melanocortin**-4 receptor (**MC4R**) knockout mice and **MC4R** antagonists have shown that weakening of **MC4R**-ergic tone increases food intake and causes obesity. In this study, we used the newly discovered selective **MC4R** antagonist HS014 for increasing food intake in free-feeding rats and evaluated the effects of the NPY Y1 receptor antagonist 1229U91 and the selective serotonin uptake inhibitor fluoxetine on this increased feeding behavior.

1229U91 (12 nmol, i.c.v.), which alone does not affect food intake, significantly attenuated the orexigenic effects of HS014, whereas 1 and 3 nmol doses of 1229U91 were ineffective. Fluoxetine, which has been shown to inhibit NPY release, inhibited spontaneous food intake and completely blocked the stimulation of food intake by HS014. These data suggest that feeding induced by weakening of the **MC4R**-ergic tone may be mediated through activation of the NPY-ergic system. This is the first report showing that physiol. feeding response evoked by **MC4R** blockage is influenced by NPY signaling. (c) 1998 Academic Press.

L23 ANSWER 18 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 129:216921 CA
TITLE: MSH-receptor subtype selective cyclic peptides
INVENTOR(S): Wikberg, Jarl; Muceniece, Ruta; Mutulis, Felikss; Prusis, Peteris; Schioth, Helgi-birgir
PATENT ASSIGNEE(S): Wapharm AB, Swed.
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9837097	A1	19980827	WO 1998-SE270	19980216 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9861274	A1	19980909	AU 1998-61274	19980216 <--
EP 1025127	A1	20000809	EP 1998-905907	19980216
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: SE 1997-620 A 19970221
WO 1998-SE270 W 19980216
OTHER SOURCE(S): MARPAT 129:216921
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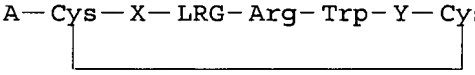

AB Title cyclic peptides I (LRG is a large amino acid; X, Y, A and B are non-cyclic peptides have 2-3, 1-2, 0-5, and 0-5 amino acid residues, resp.) were prepd. for treating conditions related to eating, body wt., motivation, learning, memory, behavior, etc. Thus, cyclo(S-S)-[Ac-Cys4,D-Cha7,Cys-NH211] .alpha.-MSH(4-10) trifluoroacetate (D-Cha = .beta.-cyclohexyl-D-alanine residue), prepd. by the solid-phase method, was assayed for binding to **melanocortin** (**MC**) receptor (MSH-receptors) subtypes: Ki = 8200, 5000, 1000, and 8600 nM corresponding to MC1, MC2, MC3, and MC4, resp.

L23 ANSWER 19 OF 78 CA COPYRIGHT 2002 ACS

ACCESSION NUMBER: 129:198133 CA
TITLE: Chimeric **melanocortin** MC1 and MC3 receptors: identification of domains participating in binding of melanocyte-stimulating hormone peptides
AUTHOR(S): Schioth, Helgi B.; Yook, Philip; Muceniece, Ruta; Wikberg, Jarl E. S.; Szardenings, Michael
CORPORATE SOURCE: Department of Pharmaceutical Pharmacology, Uppsala University, Uppsala, Swed.
SOURCE: Mol. Pharmacol. (**1998**), 54(1), 154-161
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **melanocortin** receptors MC1 and MC3 are G protein-coupled receptors that have substantial structural similarities and bind melanocyte peptides but with different affinity profiles. We constructed a series of chimeric MC1/MC3 receptors to identify the epitopes that det. their selectivities for natural melanocyte peptides and synthetic analogs. The chimeric constructs were made by a polymerase chain reaction that used identical regions in or just outside transmembranes (TM) 1, 4, and 6 and divided the receptors into four segments. Satn. and competition studies on the expressed chimeric proteins indicate that TM1, TM2, TM3, and TM7 are involved in the subtype-specific binding of melanocyte peptides to these receptors. The results support the hypothesis that TM4 and TM5 may not contribute to the ligand-binding specificity of the **MC** receptors. This is the first report to describe the subtype-specific hormone-binding domains of the **melanocortin** receptor family.

L23 ANSWER 20 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 129:198116 CA
TITLE: Evidence indicating that the extracellular loops of the mouse MC5 receptor do not participate in ligand binding
AUTHOR(S): Schioth, Helgi B.; Fredriksson, Ann; Carlsson, Cecilia; Yook, Philip; Muceniece, Ruta; Wikberg, Jarl E. S.
CORPORATE SOURCE: Biomedical Center, Department of Pharmaceutical Pharmacology, Uppsala University, Uppsala, 75 124, Swed.
SOURCE: Mol. Cell. Endocrinol. (**1998**), 139(1-2), 109-115
CODEN: MCEND6; ISSN: 0303-7207
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mMC5 receptor was cloned from a genomic library, mutated in the extracellular loops (EL's), expressed and tested for binding to MSH peptides. The EL's show low amino acid homol. within the **MC** receptor family. Two mutants of the mMC5 receptor were created to investigate the participation of these regions in ligand binding. The EL1 and EL3 were sep. altered by multiple mutagenesis so that their amino acid sequences became identical with the hMC1 receptor. The mutants were expressed in COS cells and found to bind peptide ligands in the same fashion as the wild type mMC5 receptor clone. The results indicate that the amino acids that were mutated in the mMC5 receptor do not participate in binding of MSH peptides. Comparison of the wild type mMC5 receptor with the hMC5 receptor showed that it has the same potency order for the MSH peptides but considerably higher affinity than the hMC5 receptor.

L23 ANSWER 21 OF 78 CA COPYRIGHT 2002 ACS

ACCESSION NUMBER: 129:184444 CA
TITLE: **Melanocortin** 1 receptor variants in an Irish population
AUTHOR(S): Smith, Rachel; Healy, Eugene; Siddiqui, Shazia; Flanagan, Niamh; Steijlen, Peter M.; Rosdahl, Inger; Jacques, Jon P.; Rogers, Sarah; Turner, Richard; Jackson, Ian J.; Birch-Machin, Mark A.; Rees, Jonathan L.
CORPORATE SOURCE: Department of Dermatology, University of Newcastle upon Tyne, Newcastle upon Tyne, NE2 4HH, UK
SOURCE: J. Invest. Dermatol. (**1998**), 111(1), 119-122
CODEN: JIDEAE; ISSN: 0022-202X
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The identification of an assocn. between variants in the human **melanocortin** 1 receptor (**MC1R**) gene and red hair and fair skin, as well as the relation between variants of this gene and coat color in animals, suggests that the **MC1R** is an integral control point in the normal pigmentation phenotype. In order to further define the contribution of **MC1R** variants to pigmentation in a normal population, we have looked for alterations in this gene in series of individuals from a general Irish population, in whom there is a preponderance of individuals with fair skin type. Seventy-five per cent contained a variant in the **MC1R** gene, with 30% contg. two variants. The Arg151Cys, Arg160Trp, and Asp294His variants were significantly assocd. with red hair ($p = 0.0015$, $p < 0.001$, and $p < 0.005$, resp.). Importantly, no individuals harboring two of these three variants did not have red hair, although some red-haired individuals only showed one alteration. The same three variants were also over-represented in individuals with light skin type as assessed using a modified Fitzpatrick scale. Despite these assocns. many subjects with dark hair/darker skin type harbored **MC1R** variants, but there was no evidence of any particular assocn. of variants with the darker phenotype. The Asp294His variant was similarly assocd. with red hair in a Dutch population, but was infrequent in red-headed subjects from Sweden. The Asp294His variant was also significantly assocd. with nonmelanoma skin cancer in a U.K. population. The results show that the Arg151Cys, Arg160Trp, and Asp294His variants are of key significance in detg. the pigmentary phenotype and response to UV radiation, and suggest that in many cases the red-haired component and in some cases fair skin type are inherited as a Mendelian recessive.

L23 ANSWER 22 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 129:170612 CA
TITLE: Cutaneous immunomodulation and coordination of skin stress responses by .alpha.-melanocyte-stimulating hormone
AUTHOR(S): Luger, Thomas A.; Scholzen, Thomas; Brzoska, Thomas; Becher, Eva; Slominski, Andrzej; Paus, Ralf
CORPORATE SOURCE: Ludwig Boltzmann Institute for Cell Biology and Immunobiology of the Skin, Department of Dermatology, University of Munster, Munster, D-48149, Germany
SOURCE: Ann. N. Y. Acad. Sci. (**1998**), 840(Neuroimmunomodulation), 381-394
CODEN: ANYAA9; ISSN: 0077-8923
PUBLISHER: New York Academy of Sciences
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 93 refs. The capacity of the skin immune system to mount

various types of immune responses is largely dependent on their ability to release and respond to different signals provided by immunoregulatory mediators such as cytokines. There is recent evidence that neuropeptides such as .alpha.-MSH, upon stimulation, are released by epidermal cells including keratinocytes, Langerhans cells, and melanocytes as well as immunocompetent cells. Moreover, .alpha.-MSH recently has been recognized as a potent immunomodulating agent, which inhibits the prodn. and activity of immunoregulatory and proinflammatory cytokines such as IL-1, IL-2, interferon-.gamma., downregulates the expression of costimulatory mols. (B7) on antigen-presenting cells; and recently turned out to be a potent inducer of inhibitory mediators such as cytokine synthesis inhibitory factor interleukin-10. Recently, it also was discovered that monocytes among the five known **melanocortin** (**MC**) receptors only express **MC**-1, which is specific for .alpha.-MSH. The expression of **MC**-1 on monocytes is upregulated by mitogens, endotoxins, and proinflammatory cytokines. There is also recent evidence for the in vivo relevance of the immunosuppressing capacity of .alpha.-MSH. Accordingly, in animals .alpha.-MSH has been shown to inhibit the induction of contact hypersensitivity reactions and to induce hapten-specific tolerance. These findings indicate that, in addn. to the cytokine network, neurohormones within the cutaneous microenvironment are a crucial element for the induction, elicitation, and regulation of cutaneous immune and inflammatory responses.

L23 ANSWER 23 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 129:131339 CA
TITLE: Modeling of the three-dimensional structure of the human **melanocortin** 1 receptor, using an automated method and docking of a rigid cyclic melanocyte-stimulating hormone core peptide
AUTHOR(S): Prusis, Peteris; Schioth, Helgi B.; Muceniece, Ruta; Herzyk, Pawel; Afshar, Mohammad; Hubbard, Roderick E.; Wikberg, Jarl E. S.
CORPORATE SOURCE: Pharmaceutical Pharmacology, Uppsala University, Uppsala, Swed.
SOURCE: J. Mol. Graphics Modell. (**1998**), Volume Date 1997, 15(5), 307-317
CODEN: JMGMFI; ISSN: 1093-3263
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A model is presented of the **melanocortin** 1 receptor (**MCiR**), constructed by use of an unbiased, objective method. The model is created directly from data derived from multiple sequence anal., a low-resoln. EM-projection map of rhodopsin, and the approx. membrane thickness. The model agrees well with available data concerning natural mutations of MC1Rs occurring in different species. A model is also presented of the most rigid ligand for this receptor, the cyclic pentapeptide cHFRWG, shown docked in the receptor model. The receptor-ligand complex model agrees well with available exptl. data. The ligand is located between transmembrane region 1 (TM1), TM2, TM3, TM6, and TM7 of the receptor. Multiple interactions occur between ligand and receptor, including interactions with Leu-48 (TM1), Ser-52 (TM1), Glu-55 (TM1), Asn-91 (TM2), Glu-94 (TM2), Thr-95 (TM2), Ile-98 (TM2), Asp-121 (TM3), Thr-124 (TM3), Phe-257 (TM6), Phe-283 (TM7), Asn-290 (TM7), and Asp-294 (TM7) of the receptor.

L23 ANSWER 24 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 129:118610 CA
TITLE: Molecular cloning of the chicken **melanocortin**

2 (ACTH)-receptor gene
AUTHOR(S): Takeuchi, Sakae; Kudo, Toshiyuki; Takahashi, Sumio
CORPORATE SOURCE: Faculty of Science, Department of Biology, Okayama University, Okayama, 700, Japan
SOURCE: Biochim. Biophys. Acta (**1998**), 1403(1), 102-108
CODEN: BBACAQ; ISSN: 0006-3002
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The chicken **melanocortin** 2-receptor (MC2-R) gene was isolated. It is found to be a single copy gene encoding a 357 amino acid protein, sharing 65.8-68.7% identity with mammalian counterparts. The chicken MC2-R mRNA is expressed in the adrenal and spleen, suggesting that the receptor mediates both endocrine and immunoregulatory functions of ACTH in the chicken. The amino acid sequence of the chicken MC2-R is collinear with those of other subtypes of **MC**-R, whereas all cloned mammalian MC2-Rs contain a gap in the third intracellular loop, suggesting that mammalian MC2-R mols. have evolved by lacking a part of the domain which dets. the specificity of signal transduction in G-protein coupled receptors. Interestingly, the codon usage differs dramatically between MC1-R and MC2-R in the chicken; the GC-contents at the third codon position in MC1-R and MC2-R are 94.6 and 50.6%, resp. It may reflect selective constraints on the usage of synonymous codons.

L23 ANSWER 25 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 129:63109 CA
TITLE: Discovery of novel **melanocortin4** receptor selective MSH analogs
AUTHOR(S): Schioth, Helgi B.; Mutulis, Felikss; Muceniece, Ruta; Prusis, Peteris; Wikberg, Jarl E. S.
CORPORATE SOURCE: Department of Pharmaceutical Pharmacology, Uppsala University, Uppsala, Swed.
SOURCE: Br. J. Pharmacol. (**1998**), 124(1), 75-82
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Stockton Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors synthesized a novel series of cyclic MSH analogs and tested their binding properties on cells transiently expressing the human **melanocortin1** (MC1), MC3, MC4 and MC5 receptors. The authors discovered that compds. with 26 membered rings of [Cys4,D-Nal7,Cys11].alpha.-MSH(4-11) displayed specific MC4 receptor selectivity. The preference order of the different **MC** receptor subtypes for the novel [Cys4D-Nal7Cys11].alpha.-MSH(4-11) analogs are distinct from all other known MSH analogs, particularly as they bind the MC4 receptor with high and the MC1 receptor with low relative affinities. HS964 and HS014 have 12 and 17-fold MC4/MC3 receptor selectivity, resp., which is much higher than for the previously described cyclic lactam and [Cys4,Cys10].alpha.-MSH analogs SHU9119 and HS9510. HS964 is the first substance showing higher affinity for the MC5 receptor than the MC1 receptor. 5 HS014, which was the most potent and selective MC4 receptor ligand (Ki 3.2 nM, which is .apprx.300-fold higher affinity than for .alpha.-MSH), was also demonstrated to antagonize .alpha.-MSH stimulation of cAMP in MC4 receptor transfected cells. The authors found that a compd. with a 29 membered ring of [Cys3,Nle10,D-Nal7,Cys11].alpha.-MSH(3-11) (HS010) had the highest affinity for the MC3 receptor. This is the first study to describe ligands that are truly MC4 selective and a ligand having a high affinity for the MC3 receptor. The novel compds. may be of use in clarifying the physiol. roles of the MC3, MC4 and MC5 receptors.

L23 ANSWER 26 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 129:23556 CA
TITLE: Expression of **melanocortin**-5 receptor in secretory epithelia supports a functional role in exocrine and endocrine glands
AUTHOR(S): Van der Kraan, Manou; Adan, Roger A. H.; Entwistle, Margaret L.; Gispen, Willem Hendrik; Burbach, J. Peter H.; Tatro, Jeffrey B.
CORPORATE SOURCE: Rudolf Magnus Institute Neurosciences, Department Medical Pharmacolotggy, Utrecht University, Utrecht, 3508 TA, Neth.
SOURCE: Endocrinology (**1998**), 139(5), 2348-2355
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Melanocortins** (.alpha.MSH and ACTH-related peptides) influence the physiol. functions of certain peripheral organs, including exocrine and endocrine glands. This study was designed to det. the identity and anatomical localization of the **melanocortin** receptors (**MC**-R) expressed in these organs in the rat. MC5-R mRNA was found in exocrine glands, including lacrimal, Harderian, preputial, and prostate glands an pancreas, as well as in adrenal gland, esophagus, and thymus, as demonstrated by RNase protection assays. In exocrine glands, MC5-R mRNA expression was restricted to secretory epithelia. **MC**-R protein was likewise present in secretory epithelia of exocrine glands, as detd. by 125I-labeled [Nle4,D-Phe7].alpha.MSH([125I]NDP-MSH) binding and autoradiog. in tissue sections. Specific [125I]NDP-MSH binding was also obsd. in adrenal cortex, thymus, spleen, and esophageal and trachealis muscle. **MC** receptors in these sits are accessible to circulating **MC**-R agonists in vivo, as specific binding of [125I]NDP-MSH was obsd. in exocrine and adrenal glands after systemic injection in vivo. Taken together, these findings show that the MC5 receptor is commonly and selectively expressed in exocrine glands and other peripheral organs. Based on these findings and compelling evidence from other studies, a functional coherence is suggested between central and peripheral actions of **melanocortins** and **melanocortin** receptors in physiol. functions, including thermoregulation, immunomodulation, and sexual behavior.

L23 ANSWER 27 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 129:12820 CA
TITLE: Selective antagonist for the **melanocortin** 4 receptor (HS014) increases food intake in free-feeding rats
AUTHOR(S): Kask, Ants; Rago, Lembit; Mutulis, Felikss; Pahkla, Rein; Wikberg, Jarl E. S.; Schioth, Helgi B.
CORPORATE SOURCE: Department of Pharmacology, University of Tartu, Tartu, EE-2400, Estonia
SOURCE: Biochem. Biophys. Res. Commun. (**1998**), 245(1), 90-93
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recently, we discovered a cyclic analog of MSH, HS014, which is the first selective antagonist of the MC4 receptor. We have here studied the effects of this peptide on food intake in non-deprived male rats. Vehicle or five doses of HS014 (0.1-10 nmol) were administered ICV at mid-day.

HS014 (0.33-3.3 nmol) significantly and in a dose-dependent manner increased food intake for the first 1 h. At 4 h after the injections, food intake was also significantly increased in rats treated with 1 and 3.3 nmol of HS014, whereas the lowest dose tested (0.1 nmol) was without effect. Cumulative food intake increased to 100% at 4 h after the injections. The highest dose of HS014 (10 nmol) induced sedation and inhibited feeding for first hour of testing. However, this dose also increased food consumption later. These data demonstrate that attenuation of central **melanocortinergic** tone with HS014 induces disinhibition of feeding and provides addnl. evidence for the hypothesis that activation of the MC4 receptor inhibits food intake. HS014 may be a useful tool for elucidating the role of the **MC** receptor subtypes in vivo. This is the first report demonstrating an increase in daytime food intake in free-feeding animals caused by a **MC** receptor active agent.

L23 ANSWER 28 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 128:87433 CA
TITLE: Linkage and association studies between the **melanocortin** receptors 4 and 5 genes and obesity-related phenotypes in the Quebec family study
AUTHOR(S): Chagnon, Yvon C.; Chen, Wen-Ji; Perusse, Louis; Chagnon, Monique; Nadeau, Andre; Wilkison, William O.; Bouchard, Claude
CORPORATE SOURCE: Physical Activity Sciences Laboratory, Laval University, Ste-Foy, PQ, Can.
SOURCE: Mol. Med. (N. Y.) (**1997**), 3(10), 663-673
CODEN: MOMEF3; ISSN: 1076-1551
PUBLISHER: Springer-Verlag New York Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The agouti yellow mouse shows adult onset of moderate obesity and diabetes. A depressed basal lipolytic rate in adipocytes or a decreased adrenergic tone arising from antagonizing .alpha.-MSH (MSH) activation of **melanocortin** receptors (MCR) could be at the origin of the obesity phenotype. MCR 4 and 5 (**MC4R**, **MC5R**) genes were studied in the Quebec Family Study. Sequence variations were detected by Southern blot probing of restricted genomic DNA, and mRNA tissue expression was detected by RT-PCR. Subjects with a wide range of wt. were used for single-point sib-pair linkage studies (max. of 289 sibships from 124 nuclear families). Anal. of variance across genotypes in unrelated males (n=143) and females (n=156) was also undertaken. Body mass index (BMI), sum of six skin-folds (SF6), fat mass (FM), percent body fat (%FAT), RQ (RQ), resting metabolic rate (RMR), fasting glucose and insulin, and glucose and insulin area during an oral glucose tolerance test were analyzed. **MC4R** showed polymorphism with NcoI, and **MC5R**, with PstI and PvuII, with a heterozygosity of 0.38, 0.10, and 0.20, resp. Linages were obsd. between **MC5R** and BMI (p=0.001), SF6 (p=0.005), FM (p=0.001), and RMR (p=0.002), whereas assocns. were obsd. in females between **MC5R** and BMI (p=0.003), and between **MC4R** and FM (p=0.002) and %FAT (p=0.004). After correction for multiple tests, these p values are lowered by one tenth. **MC4R** and **MC5R** mRNAs have been detected in brain, adipose tissue, and skeletal muscle. **MC4R** and **MC5R** exhibit evidence of linkage or assocns. with obesity phenotypes, but this evidence is strongest for **MC5R**.

L23 ANSWER 29 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 128:84709 CA
TITLE: .alpha.-Melanocyte-stimulating hormone and

endothelin-1 have opposing effects on melanocyte adhesion, migration, and pp125FAK phosphorylation
AUTHOR(S): Scott, Glynis; Cassidy, Linda; Abdel-Malek, Zalfa
CORPORATE SOURCE: Department of Dermatology, University of Rochester Medical Center, Rochester, NY, 14642, USA
SOURCE: Exp. Cell Res. (**1997**), 237(1), 19-28
CODEN: ECREAL; ISSN: 0014-4827
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent reports show that .alpha.-MSH is mitogenic and melanogenic for normal human melanocytes, and that this effect is mediated through binding to the **melanocortin** receptor (**MC1R**) and activation of cAMP formation. .alpha.-MSH has also been shown to induce changes in cell shape in melanocytes and melanoma cells, particularly increased dendricity, suggesting a potential role for .alpha.-MSH in melanocyte-matrix interactions and pigment transfer through reorganization of the melanocyte actin filament cytoskeleton. The authors show that the potent .alpha.-MSH analog (Nle4, D-Phe7)-.alpha.-MSH (NDP-MSH) induces reorganization of the actin stress fiber cytoskeleton in treated human melanocytes and that this reorganization is assocd. with increased adhesion to fibronectin (FN). Because most melanocyte growth factors act synergistically on melanocyte mitogenesis, the authors also sought to det. the effect of the melanocyte mitogen endothelin-1 (ET-1) on the melanocyte actin cytoskeleton, melanocyte adhesion, and melanocyte migration. The authors show that ET-1, which increases melanocyte migration on FN, has opposite effects on melanocyte adhesion to FN compared with NDP-MSH and that endothelin-1-induced actin reorganization is distinct from that obsd. following NDP-MSH treatment. Finally, the authors show that focal adhesion kinase (pp125FAK), a nonreceptor tyrosine kinase assocd. with focal contact formation and cell migration, is phosphorylated on tyrosine residues after treatment of melanocytes with ET-1, but not NDP-MSH. These data indicate that while .alpha.-MSH and ET-1 act synergistically to modulate melanocyte proliferation, they have opposite effects on melanocyte-matrix interactions.

L23 ANSWER 30 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 128:30422 CA
TITLE: Brain **melanocortin** receptors: from cloning to function
AUTHOR(S): Adan, Roger A. H.; Gispen, Willem Hendrik
CORPORATE SOURCE: Department of Medical Pharmacology, Rudolf Magnus Institute for Neurosciences, Utrecht University, Utrecht, 3584 CG, Neth.
SOURCE: Peptides (N. Y.) (**1997**), 18(8), 1279-1287
CODEN: PPTDD5; ISSN: 0196-9781
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 769 refs. The cloning of brain **melanocortin** (**MC**) receptors, the mapping of their expression pattern and the identification of **MC** receptor selective ligands have opened a new avenue towards elucidating the role of the **melanocortin** system in the brain. **MC** receptors have now been implicated in **melanocortin**-induced grooming behavior in rats, in the **melanocortin**-induced lowering of blood pressure and in the control of wt. homeostasis. Functional opioid antagonism and the anti-pyretic and anti-inflammatory effects of **melanocortins** are probably also mediated via **MC** receptors. However, the effects of **melanocortins** on avoidance behavior and the effect of .gamma.2-MSH

on increasing blood pressure are not mediated via one of the cloned brain **MC** receptors. The structure of brain **MC** receptors, their expression pattern, the **MC** receptor selective ligands and the function of **MC** receptors are briefly reviewed.

L23 ANSWER 31 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 128:10386 CA
TITLE: Selectivity of cyclic [D-Nal7] and [D-Phe7] substituted MSH analogs for the **melanocortin** receptor subtypes
AUTHOR(S): Schioth, Helgi B.; Muceniece, Ruta; Mutulis, Felikss; Prusis, Peteris; Lindeberg, Gunnar; Sharma, Shubh D.; Hruby, Victor J.; Wikberg, Jarl E. S.
CORPORATE SOURCE: Department of Pharmaceutical Pharmacology and Department of Medicinal and Physiological Chemistry, Uppsala University, Uppsala, Swed.
SOURCE: Peptides (Tarrytown, N. Y.) (**1997**), 18(7), 1009-1013
CODEN: PPTDD5; ISSN: 0196-9781
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The binding of the 2 cyclic lactam MSH (4-10) analogs (melanotan II, SHU 9119), and 5 cyclic [Cys4,Cys10].alpha.-MSH analogs were tested on cells transiently expressing the human MC1, MC3, MC4 and MC5 receptors. The results indicate a differential importance of the C-terminal (Lys-Pro-Val) and N-terminal (Ser-Tyr-Ser) of cyclic [Cys4,Cys10].alpha.-MSH analogs in binding to the **MC** receptor subtypes. Substitution of D-Phe7 by D-Nal(2')7 in both the cyclic lactam MSH (4-10) and the cyclic disulfide MSH (4-10) analogs resulted in a shift in favor of selectivity for the MC4 receptor; the disulfide analog, [Cys4,D-Nal(2')7 Cys10].alpha.-MSH (4-10) (HS 9510), showing the highest selectivity for the MC4 receptor among all the substances tested. However, the cyclic lactams displayed an over all higher affinity for the **MC** receptors, than any of the cyclic disulfide MSH (4-10) analogs.

L23 ANSWER 32 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 127:329902 CA
TITLE: Antagonism of central **melanocortin** receptors in vitro and in vivo by Agouti-related protein
AUTHOR(S): Ollmann, Michael M.; Wilson, Brent D.; Yang, Ying-Kui; Kerns, Julie A.; Chen, Yanru; Gantz, Ira; Barsh, Gregory S.
CORPORATE SOURCE: Dep. Pediatr. Genet., Howard Hughes Med. Inst., Stanford Univ. Sch. Med., Stanford, CA, 94305, USA
SOURCE: Science (Washington, D. C.) (**1997**), 278(5335), 135-138
CODEN: SCIEAS; ISSN: 0036-8075
PUBLISHER: American Association for the Advancement of Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Expression of Agouti protein is normally limited to the skin where it affects pigmentation, but ubiquitous expression causes obesity. An expressed sequence tag was identified that encodes Agouti-related protein, whose RNA is normally expressed in the hypothalamus and whose levels were increased eightfold in ob/ob mice. Recombinant Agouti-related protein was a potent, selective antagonist of **Mc3r** and **Mc4r**, **melanocortin** receptor subtypes implicated in wt. regulation. Ubiquitous expression of human AGRP complementary DNA in transgenic mice caused obesity without altering pigmentation. Thus, Agouti-related

protein is a neuropeptide implicated in the normal control of body wt. downstream of leptin signaling.

L23 ANSWER 33 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 127:326944 CA
TITLE: Synthetic peptides derived from the melanocyte-stimulating hormone receptor **MC1R** can stimulate HLA-A2-restricted cytotoxic T lymphocytes that recognize naturally processed peptides on human melanoma cells
AUTHOR(S): Salazar-Onfray, Flavio; Nakazawa, Tsutomu; Chhajlani, Vijay; Petersson, Max; Karre, Klas; Masucci, Giuseppe; Celis, Esteban; Sette, Alessandro; Southwood, Scott; Appella, Ettore; Kiessling, Rolf
CORPORATE SOURCE: Microbiology and Tumor Biology Center, Karolinska Institute, Stockholm, S-171 77, Swed.
SOURCE: Cancer Res. (**1997**), 57(19), 4348-4355
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human melanoma-specific HLA-A2 restricted CTLs have recently been shown to recognize antigens expressed by melanoma lines and normal melanocytes, including Melan-A/Mart-1, gp100, gp75, and tyrosinase. Herein, the authors define HLA-A2-restricted CTL epitopes from a recently cloned **melanocortin** 1 receptor (**MC1R**), which belongs to a new subfamily of the G-protein-coupled receptors expressed on melanomas and melanocytes. Thirty-one **MC1R**-derived peptides were selected on the basis of HLA-A2-specific motifs and tested for their HLA-A2 binding capacity. Of a group of 12 high or intermediate HLA-A2 binding peptides, three nonamers, MC1R244 (TILLGIFFL), MC1R283 (FLALIICNA), and MC1R291 (AIIDPLIYA), were found to induce peptide-specific CTLs from peripheral blood mononuclear cells of healthy HLA-A2+ donors after repeated in vitro stimulation with peptide-pulsed antigen-presenting cells. The CTLs raised against these three HLA-A2+-restricted peptides could recognize naturally processed peptides from HLA-A2+ melanomas and from Cos7 cells cotransfected with **MC1R** and HLA-A2. CTLs induced by the MC1R291 peptide (but not induced or induced only to a very low extent by the other two MCR1 peptide epitopes) showed cross-reactions with two other members of the **melanocortin** receptor family, which are more broadly expressed on other tissues. Taken together, the authors' findings have implications in relation both to autoimmunity and immunotherapy of malignant melanomas.

L23 ANSWER 34 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 127:326665 CA
TITLE: The **melanocortin** 1, 3, 4 or 5 receptors do not have a binding epitope for ACTH beyond the sequence of .alpha.-MSH
AUTHOR(S): Schioth, H. B.; Muceniece, R.; Larsson, M.; Wikberg, J. E. S.
CORPORATE SOURCE: Dep. Pharmaceutical Pharmacology, Uppsala Univ., Uppsala, Swed.
SOURCE: J. Endocrinol. (**1997**), 155(1), 73-78
CODEN: JOENAK; ISSN: 0022-0795
PUBLISHER: Journal of Endocrinology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB ACTH(1-39), and several shorter N- and/or C-terminally truncated fragments of ACTH, with and without N-terminal acetylation and/or C-terminal

amidation, were tested for binding on a single eukaryotic cell line transiently and independently expressing the **melanocortin** MC1, MC3, MC4 and MC5 receptors. The results show that none of these **MC** receptors has specific binding epitopes for the ACTH peptides beyond the amino acid sequence of .alpha.-MSH, when tested for their ability to compete with 125I-labeled [Nle4,D-Phe7].alpha.-MSH and ACTH. The MC3 receptor favors the natural desacetylated N-terminal end of the ACTH peptides, and it has generally more than 10-fold higher affinity for the ACTH peptides than the MC4 receptor. Considering earlier anatomical localization data, together with the present data, we suggest that the MC3 receptor is the most likely candidate of the **MC** receptors to mediate the short-loop neg. feedback release of corticotrophin-releasing factor (CRF) caused by ACTH/MSH peptides.

L23 ANSWER 35 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 127:315008 CA
TITLE: Characterization of ACTH peptides in human skin and their activation of the **Melanocortin**-1 receptor
AUTHOR(S): Wakamatsu, Kazumasa; Graham, Alison; Cook, David; Thody, Anthony J.
CORPORATE SOURCE: Departments of 'Dermatology and Clinical Biochemistry, University of Newcastle upon Tyne, Newcastle upon Tyne, NE2 4HH, UK
SOURCE: Pigm. Cell Res. (**1997**), 10(5), 288-297
CODEN: PCREEA; ISSN: 0893-5785
PUBLISHER: Munksgaard
DOCUMENT TYPE: Journal
LANGUAGE: English

AB .alpha.-MSH is a proopiomelanocortin (POMC)-derived peptide, which is produced in the pituitary and at other sites including the skin. It has numerous effects and in the skin has a pigmentary action through the activation of the **melanocortin**-1 (**MC**-1) receptor, which is expressed by melanocytes. Recent evidence suggests that the related POMC peptides such as adrenocorticotrophin (ACTH), which is the precursor of .alpha.-MSH, is also an agonist at the **MC**-1 receptor. By using immunocytochem., we confirmed the presence of .alpha.-MSH in human skin where staining was evident in keratinocytes and esp. strong in melanocytes and possibly Langerhans cells. ACTH was also present and tended to show the strongest reaction in differentiated keratinocytes. Immunostaining was also obsd. for the prohormone convertases, PC1 and PC2, which are involved in the formation of ACTH and its cleavage to .alpha.-MSH, resp. The amts. of immunoreactive ACTH exceeded those of .alpha.-MSH. Using HPLC we identified for the first time the presence of ACTH1-39, ACTH1-17, ACTH1-10, acetylated ACTH1-10, .alpha.-MSH, and desacetyl .alpha.-MSH in epidermis and in cultured keratinocytes. The ability of these peptides to activate the human **MC**-1 receptor was examd. in HEK 293 cells that had been transfected with the receptor. All peptides increased adenylate cyclase in these cells with the following order of potency: ACTH1-17 > .alpha.-MSH > ACTH1- 39 > desacetyl a-MSH > acetylated ACTH1-10 > ACTH1-10. ACTH1-17 also increased the dendricity and melanin content of cultured human melanocytes indicating that the peptide was able to activate **MC** -1 receptors when present in their normal location. However, as found with .alpha.-MSH, not all cultures were responsive and, as we have previously suggested, we suspect that this was the result of changes at the **MC**-1 receptor. Nevertheless, it would appear that ACTH peptides can serve as natural ligands of the **MC**-1 receptor on human melanocytes and their presence in the skin suggests that, together with .alpha.-MSH, they may have a role in the regulation of human

melanocytes.

L23 ANSWER 36 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 127:314975 CA
TITLE: Immunohistochemical detection of the **melanocortin** 1 receptor in human testis, ovary, and placenta using specific monoclonal antibody
AUTHOR(S): Thornwall, Madeleine; Dimitriou, Alexandros; Xu, Xiaolin; Larsson, Erik; Chhajlani, Vijay
CORPORATE SOURCE: Biomedical Center, Univ. Uppsala, Uppsala, Swed.
SOURCE: Horm. Res. (**1997**), 48(5), 215-218
CODEN: HRMRA3; ISSN: 0301-0163
PUBLISHER: Karger
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The immunohistochem. detection of the **melanocortin** 1 receptor (**MC1R**) protein in human gonadal tissues was describe using a specific monoclonal antibody. The **MC1R** was present in Leydig's cells in testis, in lutein cells in the corpus luteum, and in the nucleus of the trophoblastic cells of the placenta. This is the 1st report demonstrating the presence of **MC1R** protein in gonadal cells.

L23 ANSWER 37 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 127:305781 CA
TITLE: Genetic studies of the mouse mutations mahogany and mahoganoid
AUTHOR(S): Miller, K. A.; Gunn, T. M.; Carrasquillo, M. M.; Lamoreux, M. L.; Galbraith, D. B.; Barsh, G. S.
CORPORATE SOURCE: Departments of Pediatrics and Genetics, Stanford University School of Medicine, Stanford, CA, 94305-5428, USA
SOURCE: Genetics (**1997**), 146(4), 1407-1415
CODEN: GENTAE; ISSN: 0016-6731
PUBLISHER: Genetics Society of America
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The mouse mutations mahogany (mg) and mahoganoid (md) are neg. modifiers of the Agouti coat color gene, which encodes a paracrine signaling mol. that induces a switch in melanin synthesis from eumelanin to pheomelanin. Animals mutant for md or mg synthesize very little or no pheomelanin depending on Agouti gene background. The Agouti protein is normally expressed in the skin and acts as an antagonist of the melanocyte receptor for .alpha.-MSH (**Mc1r**); however, ectopic expression of Agouti causes obesity, possibly by antagonizing **melanocortin** receptors expressed in the brain. To investigate where md and mg lie in genetic pathway with regard to Agouti and **Mc1r** signaling, we detd. the effects of these mutations in animals that carried either a loss-of-function **Mc1r** mutation (recessive yellow, Mc1re) or a gain-of-function Agouti mutation (lethal yellow, Ay). We found that the Mc1re mutation suppressed the effects of md and mg, but that md and mg suppressed the effects of Ay on both coat color and obesity. Plasma levels of .alpha.-MSH and of ACTH were unaffected by md or mg. These results suggest that md and mg interfere directly with Agouti signaling, possibly at the level of protein prodn. or receptor regulation.

L23 ANSWER 38 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 127:288382 CA
TITLE: ART (protein product of agouti-related transcript) as an antagonist of **MC**-3 and **MC**-4 receptors

AUTHOR(S): Fong, Tung Ming; Mao, Cheri; Macneil, Tanya; Kalyani, Rubana; Smith, Tim; Weinberg, David; Tota, Michael R.; Van Der Ploeg, Lex H. T.
CORPORATE SOURCE: Merck Research Laboratories, R80M-213, Rahway, NJ, 07065, USA
SOURCE: Biochem. Biophys. Res. Commun. (**1997**), 237(3), 629-631
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The mRNA encoding an agouti related protein (ART) of unknown biochem. function was previously reported to be up-regulated in the hypothalamus of two genetically obese mouse strains. We have expressed human ART as a secreted protein in COS-7 cells, and show that recombinant ART is functionally active in inhibiting the binding of a radiolabeled .alpha.-MSH analog to the human **melanocortin**-3 (**MC**-3) and **melanocortin**-4 (**MC**-4) receptors, while it is not a potent inhibitor of the human **melanocortin**-5 (**MC**-5) receptor. ART is an antagonist of the human **MC**-3 and **MC**-4 receptors as detd. in functional assay. ART appears to be approx. 100-fold more potent than agouti with ref. to the **MC**-3 and **MC**-4 receptor binding affinity. These data suggest that ART may be a physiol. regulator of feeding behavior.

L23 ANSWER 39 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 127:288302 CA
TITLE: Molecular basis for the interaction of [Nle4,D-Phe7]-melanocyte stimulating hormone with the human **melanocortin**-1 receptor (melanocyte .alpha.-MSH receptor)
AUTHOR(S): Yang, Ying-Kui; Dickinson, Chris; Haskell-Luevano, Carrie; Gantz, Ira
CORPORATE SOURCE: Department of Internal Medicine, University of Michigan Medical School and Veterans Administration Medical Center, Ann Arbor, MI, 48109-0682, USA
SOURCE: J. Biol. Chem. (**1997**), 272(37), 23000-23010
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The **melanocortin**-1 receptor (**MC1R**) is a seven-transmembrane (TM) G-protein-coupled receptor whose natural ligands are the **melanocortin** peptides, ACTH, and .alpha.-, .beta.-, and .gamma.- MSH. To test a previously constructed three-dimensional model of the mol. interaction between the long-acting, superpotent .alpha.-MSH analog [Nle4,D-Phe7]-.alpha.-MSH (NDP-MSH) and the human **MC1R** we examd. the effects of site-directed receptor mutagenesis on the binding affinity and potency of NDP-MSH. In addn., we also examd. the effects of these same mutations on the binding affinity and potency of the structurally related agonists .alpha.-MSH, .gamma.-MSH, and Ac-Nle-cyclic-[Asp,His,D-Phe,Arg,Trp,Lys]-NH2 (MT-II). Mutagenesis of acidic receptor residues Glu94 in TM2 and Asp117 or Asp121 in TM3 significantly altered the binding affinity and potency of all four agonists suggesting that these receptor residues are important to the ligand-receptor interactions of all. A disproportionate change in agonist potency vs. affinity obsd. with simultaneous mutation of these acidic residues (mutant constructs D117A/D121A or E94A/D117A/D121A) or introduction of a single pos. charge (mutant construct D121K) also

implicates these residues in receptor activation. In addn., results from the individual mutation of arom. receptor residues Phe175, Phe196, and Phe257, and simultaneous mutation of multiple TM4, -5, and -6 tyrosine and phenylalanine residues suggests that arom.-arom. ligand-receptor interactions also participate in binding these **melanocortins** to the **MC1R**. These expts. appear to have identified some of the crit. receptor residues involved in the ligand-receptor interactions between these **melanocortins** and the hMC1R.

L23 ANSWER 40 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 127:273643 CA
TITLE: Identification of an obesity quantitative trait locus on mouse chromosome 2 and evidence of linkage to body fat and insulin on the human homologous region 20q
AUTHOR(S): Lembertas, Audra V.; Perusse, Louis; Chagnon, Yvon C.; Fisler, Janis S.; Warden, Craig H.; Purcell-Huynh, Deborah A.; Dionne, France T.; Gagnon, Jacques; Nadeau, Andre; Lusis, Aldons J.; Bouchard, Claude
CORPORATE SOURCE: Department of Medicine, Department of Microbiology and Molecular Genetics, University of California, Los Angeles, CA, 90095-1679, USA
SOURCE: J. Clin. Invest. (**1997**), 100(5), 1240-1247
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Chromosomal synteny between the mouse model and humans was used to map a gene for the complex trait of obesity. Anal. of NZB/BINJ .times. SM/J intercross mice located a quant. trait locus (QTL) for obesity on distal mouse chromosome 2, in a region syntenic with a large region of human chromosome 20, showing linkage to percent body fat (likelihood of the odds [LOD] score 3.6) and fat mass (LOD score 4.3). The QTL was confirmed in a congenic mouse strain. To test whether the QTL contributes to human obesity, we studied linkage between markers located within a 52-cM region extending from 20p12 to 20q13.3 and measures of obesity in 650 French Canadian subjects from 152 pedigrees participating in the Quebec Family Study. Sibpair anal. based on a max. of 258 sib pairs revealed suggestive linkages between the percentage of body fat ($P < 0.004$), body mass index ($P < 0.008$), and fasting insulin ($P < 0.0005$) and a locus extending approx. from ADA (the adenosine deaminase gene) to **MC3R** (the **melanocortin** 3 receptor gene). These data provide evidence that a locus on human chromosome 20q contributes to body fat and insulin in a human population, and demonstrate the utility of using interspecies syntenic relationships to find relevant disease loci in humans.

L23 ANSWER 41 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 127:258646 CA
TITLE: Gene specific universal mammalian sequence-tagged sites
INVENTOR(S): Brewer, George J.; Venta, Patrick J.; Yuzbasiyan-Gurkan, Vilma
PATENT ASSIGNEE(S): Regents of the University of Michigan, USA; Board of Trustees Operating Michigan State University; Brewer, George J.; Venta, Patrick J.; Yuzbasiyan-Gurkan, Vilma
SOURCE: PCT Int. Appl., 26 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9731012	A1	19970828	WO 1997-US2403	19970218 <--
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9719598	A1	19970910	AU 1997-19598	19970218 <--
PRIORITY APPLN. INFO.:			US 1996-12061	19960222
			WO 1997-US2403	19970218

AB Primer sets which amplify conserved regions of specific genes across mammalian species are provided. Such genetic markers based on PCR primers are called sequence-tagged sites (STSs) or sequence-tagged site primers. Because the primer sets may be used to locate genes across mammalian species, such primer sets are referred to as universal mammalian sequence-tagged site (UM-STS) primers. The methods used to design the primer sets as well as methods of making and using the primer sets are also provided. Primers were designed to genes where the intron-exon structure was known in at least one species and where the nucleotide sequence was known in at least two species (the index species) that were not closely related. Tandemly duplicated genes known to have undergone gene conversion in any species were avoided. Primers were generally designed so that the amplified product contained an intron. Primers were designed to highly conserved nucleotide sequences contained within coding regions, and addnl. considerations taken into account were: degeneracy of underlying codons, placement of the 3' end of the primer with respect to amino acid mutability, and conservation of amino acids within multigene families when possible. All sets of primer pairs were designed to have approx. the same annealing temp. in anticipation of performing multiplex amplifications. The universal utility of these primers was studied on the DNAs from mammals representing several different orders using the primer sets under the reaction conditions (termed Zoo PCRs) that were found to amplify canine sequences.

L23 ANSWER 42 OF 78 CA COPYRIGHT 2002 ACS

ACCESSION NUMBER:	127:243400 CA
TITLE:	Human dermal microvascular endothelial cells express the **melanocortin** receptor type 1 and produce increased levels of IL-8 upon stimulation with .alpha.-melanocyte-stimulating hormone
AUTHOR(S):	Hartmeyer, Mechthild; Scholzen, Thomas; Becher, Eva; Bhardwaj, Ranjit S.; Schwarz, Thomas; Luger, Thomas A.
CORPORATE SOURCE:	Dep. Dermatology, Ludwig Boltzmann Inst. Cell Biology & Immunobiology Skin, Univ. Munster, Munster, Germany
SOURCE:	J. Immunol. (**1997**), 159(4), 1930-1937 CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER:	American Association of Immunologists
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Pro-opiomelanocortin (POMC)-derived peptides such as .alpha.-MSH (.alpha.-MSH) recently have been recognized as mediators with potent immunomodulating and anti-inflammatory properties. Their effects are mediated via different protein G-couple **melanocortin** (**MC**) receptors that are capable to bind one or more POMC-derived peptides. Among these receptors, **MC**-1 is specific for .alpha.-MSH and

ACTH. The purpose of the present study was to investigate whether **MC** receptors are expressed on normal human dermal microvascular endothelial cells (HDMEC) as well as transformed human dermal microvascular endothelial cells (HMEC-1). Using semiquant. reverse transcriptase-PCR and **MC** receptor-specific primers, both HDMEC and HMEC-1 were found to express **MC**-1 constitutively. In addn., **MC**-1 expression was increased upon stimulation with IL-1.beta. or .alpha.-MSH itself. Other known **MC** receptors were neither detectable in unstimulated nor in IL-1.beta.- or .alpha.-MSH-stimulated cells. The binding of .alpha.-MSH by HMEC-1 was specific and saturable as demonstrated by competitive and satn.-binding studies with 125I-labeled .alpha.-MSH (Kd: 1.1 nM). To evaluate the physiol. relevance of **MC**-1 expression, HMEC-1 were treated with various concns. of .alpha.-MSH (10-15-10-6 M) and were investigated for their cytokine-producing capacity. .alpha.-MSH (10-10-10-8 M) significantly up-regulated IL-8 release and mRNA expression by HMEC-1. In contrast, the prodn. of IL-1 or IL-6 by HMEC-1 was not affected upon treatment with .alpha.-MSH. These data provide first evidence that HDMEC express functional **MC** receptors. Therefore, .alpha.-MSH, which is released in the skin during cutaneous inflammation via inducing chemokines may represent an important signal required for leukocyte-endothelial cell interaction.

L23 ANSWER 43 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 127:203857 CA
TITLE: Molecular screening of the human **melanocortin** -4 receptor gene. Identification of a missense variant showing no association with obesity, plasma glucose, or insulin
AUTHOR(S): Gotoda, T.; Scott, J.; Aitman, T. J.
CORPORATE SOURCE: Royal Postgraduate Medical School, Hammersmith Hospital, London, W12 0NN, UK
SOURCE: Diabetologia (**1997**), 40(8), 976-979
CODEN: DBTGAJ; ISSN: 0012-186X
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Disruption of the **melanocortin**-4 (**MC**-4) receptor gene in mice results in maturity-onset obesity, hyperinsulinemia and hyperglycemia. These phenotypes are characteristic of human obesity that frequently accompanies non-insulin-dependent diabetes. It is therefore possible that human **MC**-4 receptor gene mutations contribute to human obesity. To test this possibility, we examd. by DNA sequencing the entire coding region of the human **MC**-4 receptor gene in 40 morbidly obese (BMI >35 kg/m2) white British males and examd. the 5'- and 3'flanking regions in 20 out of these obese subjects. We also sequenced all these regions in 10 lean (BMI <18 kg/m2) white British males for a ref. We identified a single nucleotide substitution that replaces valine with isoleucine at codon 103, in two obese subjects in the heterozygous state. No other nucleotide alterations were found. The prevalence of this missense variant was studied in 322 white British males (190 with BMI >28 kg/m2 and 132 with BMI < 22kg/m2) selected from a population-based epidemiol. survey. In these subjects, no homozygotes for the isoleucine allele were found. The frequency of heterozygotes was similar (4.2 vs. 4.5%) in the two groups and there was no significant difference in BMI, total skinfold thickness, plasma insulin and glucose levels between heterozygotes and codon-103 valine homozygotes in either group. These results suggest that coding sequence mutations in the **MC**-4 receptor gene are unlikely to be a major cause of human obesity, at least in white British males [Diabetologia (1997) 40: 976-979].

L23 ANSWER 44 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 127:200252 CA
TITLE: Effect of POMC1-76, its C-terminal fragment .gamma.3-MSH and anti-POMC1-76 antibodies on DNA replication in lactotrophs in aggregate cell cultures of immature rat pituitary
AUTHOR(S): Tilemans, Diane; Ramaekers, Dirk; Andries, Maria; Denef, Carl
CORPORATE SOURCE: Laboratory of Cell Pharmacology, University of Leuven Medical School, Louvain, B 3000, Belg.
SOURCE: J. Neuroendocrinol. (**1997**), 9(8), 627-637
CODEN: JOUNE2; ISSN: 0953-8194
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Treatment of aggregate cell cultures of 14-day-old rat pituitary for 40 h with purified human (h) POMC1-78 dose-dependently augmented the no. of DNA replicating lactotrophs as estd. by autoradiog. of [3H]-thymidine (3H-T) incorporation in cells immunostained for prolactin (PRL). No such effect was seen on the total no. of 3H-T labeled cells (the majority of which did not contain any pituitary hormone in a detectable amt.) or on the total no. of lactotrophs. The effect of hPOMC1-76 on 3H-T incorporation in lactotrophs was blocked by concomitant treatment with anti-hPOMC1-76 monoclonal and polyclonal antibodies cross-reactive with rat POMC1-74. The latter anti-hPOMC1-76 antibodies also decreased the no. of 3H-T incorporating lactotrophs in the absence of hPOMC1-76 .gamma.3-MSH, which is the C-terminal domain of hPOMC1-76, mimicked the effect of hPOMC1-76 on 3H-T incorporation in lactotrophs but its potency was lower than that of hPOMC1-76. Other **melanocortin** (**MC**) peptides such as .alpha.- and .beta.-MSH were also effective but were less potent than .gamma.3-MSH. The difference in potency was not due to partial degrdn. of the peptides. The hPOMC1-76 did not affect 3H-T incorporation in other pituitary cell types. In contrast, .gamma.3-MSH also augmented the no. of 3H-T labeled somatotrophs and thyrotrophs. In the embryonic kidney 293 cell line stably transfected with the **MC**-3 receptor, .gamma.3-MSH (10 nM) augmented cAMP formation up to 30 times. In contrast, hPOMC1-76 (100 nM) was inactive in this test system, indicating this peptide is not an agonist at the **MC**-3 receptor. The present investigation further supports the role of rat POMC1-74 as a paracrine growth factor in the development of lactotrophs. The active core of POMC1-76 does not seem to be restricted to its C-terminal domain .gamma.3-MSH as the latter peptides displays a growth promoting effect that is different from that of POMC1-76: it is less potent, it is not specific for lactotrophs and whereas the effect of .gamma.3-MSH may be mediated by the **MC**-3 receptor that of POMC1-76 is not.

L23 ANSWER 45 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 127:185882 CA
TITLE: The role of .alpha.-melanocyte-stimulating hormone in cutaneous biology
AUTHOR(S): Luger, Thomas A.; Scholzen, Thomas; Grabbe, Stephan
CORPORATE SOURCE: Ludwig Boltzmann Institute for Cell Biology and Immunobiology of the Skin, Department of Dermatology, University of Munster, Munster, D-48149, Germany
SOURCE: J. Invest. Dermatol. Symp. Proc. (**1997**), 2(1), 87-93
CODEN: JDSPFO; ISSN: 1087-0024
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review, with .apprx.90 refs. .alpha.-MSH is a neuroimmunomodulating peptide that was recently detected in many non-pituitary tissues including the skin. Accordingly, epidermal cells such as keratinocytes and melanocytes (as well as dermal cells such as fibroblasts and endothelial cells), after stimulation with pro-inflammatory cytokines or UV light, synthesize, and release .alpha.MSH. The effects of these peptides are mediated through specific **melanocortin** (**MC**) receptors that can be detected on immunocompetent and inflammatory cells as well as on keratinocytes, melanocytes, fibroblasts, and endothelial cells. In addn. to its well known pigment-inducing capacity, .alpha.MSH is able to modulate keratinocyte proliferation and differentiation. Endothelial cell and fibroblast cytokine prodn. and fibroblast collagenase prodn. are also regulated by .alpha.MSH. The immunosuppressive capacity of .alpha.MSH is mediated mainly through its effects on monocyte and macrophage functions. Accordingly, .alpha.MSH downregulates the prodn. of pro-inflammatory cytokines and accessory mols. on antigen-presenting cells. The prodn. of suppressor factors such as IL-10, however, is upregulated by .alpha.MSH. The in vivo relevance of these data is documented by the finding that systemic application of .alpha.MSH inhibits the induction and the elicitation of murine contact hyper-sensitivity and induces hapten-specific tolerance. These findings indicate that .alpha.MSH is part of the mediator network that regulates cutaneous inflammation and hyper-proliferative skin diseases.

L23 ANSWER 46 OF 78 CA COPYRIGHT 2002 ACS

ACCESSION NUMBER: 127:131121 CA

TITLE: Deletions of the N-terminal regions of the human **melanocortin** receptors

AUTHOR(S): Schioeth, Helgi B.; Petersson, Susanna; Muceniece, Ruta; Szardenings, Michael; Wikberg, Jarl E. S.

CORPORATE SOURCE: Department of Pharmaceutical Pharmacology, Biomedical Center, Uppsala University, Box 591, 75124, Uppsala, Swed.

SOURCE: FEBS Lett. (**1997**), 410(2,3), 223-228
CODEN: FEBLAL; ISSN: 0014-5793

PUBLISHER: Elsevier

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The non-homologous N-terminal regions of four human **melanocortin** (**MC**) receptors were truncated to investigate their putative participation in ligand binding. Eleven constructs were made, where different nos. of residues from the N terminus were deleted. These constructs were used for transient expression expts. in COS cells and analyzed by ligand binding. The results show that 27, 25, 28, and 20 amino acids could be deleted from the N terminus of the human MC1, MC3, MC4 and MC5 receptors, resp., including all potential N-terminal glycosylation sites in the MC1 and the MC4 receptors, without affecting ligand binding or expression levels. The results indicate that the N-terminal regions of the human MC1, MC3, MC4 and MC5 receptors, do not play an important role for the ligand binding properties of these receptors.

L23 ANSWER 47 OF 78 CA COPYRIGHT 2002 ACS

ACCESSION NUMBER: 127:117583 CA

TITLE: Selectivity of [Phe-I7], [Ala6], and [D-Ala4,Gln5,Tyr6] substituted ACTH(4-10) analogs for the **melanocortin** receptors

AUTHOR(S): Schioth, Helgi B.; Muceniece, Ruta; Wikberg, Jarl E. S.

CORPORATE SOURCE: Department Pharmaceutical Pharmacology, Uppsala University, Uppsala, Swed.
SOURCE: Peptides (Tarrytown, N. Y.) (**1997**), 18(5), 761-763
CODEN: PPTDD5; ISSN: 0196-9781
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We tested [Ala6]ACTH(4-10) and [Phe-I7]ACTH(4-10) (putative **MC** receptor antagonists), [D-Ala4,Gln5,Tyr6]ACTH(4-10) (BIM 22015), and ACTH(4-10) with radioligand binding using transiently expressed human MC1, MC3, MC4, and MC5 receptors. [Phe-I7]ACTH(4-10) had higher affinity for the MC3, MC4, and MC5 receptors but lower for the MC1 compared to ACTH(4-10). [Ala6]ACTH(4-10) did not bind the MC1 receptor but had highest affinity for the MC4 receptor. The data indicate that the His6 has a specially important role in binding to the MC1 receptor. The BIM 22015 did not bind to these **MC** receptor subtypes, which indicates that the neurotrophic and myotrophic properties that are attributed to this peptide are mediated by some other receptor.

L23 ANSWER 48 OF 78 CA COPYRIGHT 2002 ACS

ACCESSION NUMBER: 127:76300 CA

TITLE: Agouti signaling protein inhibits melanogenesis and the response of human melanocytes to .alpha.-melanotropin

AUTHOR(S): Suzuki, Itaru; Tada, Akihiro; Ollmann, Michael M.; Barsh, Gregory S.; Im, Sungbin; Lamoreux, M. Lynn; Hearing, Vincent J.; Nordlund, James J.; Abdel-Malek, Zalfa A.
CORPORATE SOURCE: POLA Laboratories, Yokohama, Japan

SOURCE: J. Invest. Dermatol. (**1997**), 108(6), 838-842
CODEN: JIDEAE; ISSN: 0022-202X
PUBLISHER: Blackwell
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In mouse follicular melanocytes, the switch between eumelanin and pheomelanin synthesis is regulated by the extension locus, which encodes the **melanocortin**-1 receptor (**MC1R**) and the agouti locus, which encodes a novel paracrine-signaling mol. that inhibits binding of **melanocortins** to the **MC1R**. Human melanocytes express the **MC1R** and respond to melanotropins with increased proliferation and eumelanogenesis, but a potential role for the human homolog of agouti-signaling protein, ASIP, in human pigmentation has not been investigated. Here we report that ASIP blocked the binding of .alpha.-MSH to the **MC1R** and inhibited the effects of .alpha.-MSH on human melanocytes. Treatment of human melanocytes with 1 nM-10 nM recombinant mouse or human ASIP blocked the stimulatory effects of .alpha.-MSH on cAMP accumulation, tyrosinase activity, and cell proliferation. In the absence of exogenous .alpha.-MSH, ASIP inhibited basal levels of tyrosinase activity and cell proliferation and reduced the level of immunoreactive tyrosinase-related protein-1 (TRP-1) without significantly altering the level of immunoreactive tyrosinase. In addn., ASIP blocked the stimulatory effects of forskolin or dibutyryl cAMP, agents that act downstream from the **MC1R**, on tyrosinase activity and cell proliferation. These results demonstrate that the functional relation between the agouti and **MC1R** gene products is similar in mice and humans and suggest a potential physiol. role for ASIP in regulation of human pigmentation.

L23 ANSWER 49 OF 78 CA COPYRIGHT 2002 ACS

ACCESSION NUMBER: 127:76156 CA
TITLE: Discovery of Prototype Peptidomimetic Agonists at the Human **Melanocortin** Receptors **MC1R** and **MC4R**
AUTHOR(S): Haskell-Luevano, Carrie; Hendrata, Siska; North, Cheryl; Sawyer, Tomi K.; Hadley, Mac E.; Hruby, Victor J.; Dickinson, Chris; Gantz, Ira
CORPORATE SOURCE: Departments of Internal Medicine Pediatrics and Surgery, University of Michigan Medical Center, Ann Arbor, MI, 48109, USA
SOURCE: J. Med. Chem. (**1997**), 40(14), 2133-2139
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB [Nle4,DPhe7]-.alpha.-MSH (NDP-MSH), a highly potent analog of .alpha.-MSH, possesses nanomolar efficacies at all the **melanocortin** receptor subtypes except the **MC2R**. Evaluation of the **melanocortin** "message" sequence of [Nle4,DPhe7]-.alpha.-MSH was performed on the human **melanocortin** receptor subtypes designated hMC1, hMC3R, hMC4R, and hMC5R. Tetrapeptides and tripeptides were stereochem. modified to explore topochem. preferences at these receptors and to identify lead peptides possessing agonist activity and subtype selectivity. Four peptides were discovered to only bind to the hMC1 and hMC4 receptor subtypes. The tetrapeptide Ac-His-DPhe-Arg-Trp-NH2 possessed 0.6 .mu.M binding affinity at the hMC1R, 1.2 .mu.M binding affinity at the hMC4R, and agonist activity at both receptors. The tripeptides Ac-DPhe-Arg-Trp-NH2 and Ac-DPhe-Arg-DTrp-NH2 possessed 2.0 and 9.1 .mu.M binding affinities, resp., only at the hMC4R, and both compds. effected agonist activity. The tetrapeptide Ac-His-Phe-Arg-DTrp-NH2 possessed 6.3 .mu.M affinity and full agonist activity at the hMC1R, while only binding 7% at the hMC3R, 36% at the hMC4R, and 11% at the hMC5R at a maximal concn. of 10 .mu.M. These data demonstrate that the His-Phe-Arg-Trp message sequence of the **melanocortin** peptides does not bind and stimulate each **melanocortin** receptor in a similar fashion, as previously hypothesized. Addnl., this study identified the simplest structural agonists for the hMC1R and hMC4R receptors reported to date.

L23 ANSWER 50 OF 78 CA COPYRIGHT 2002 ACS
ACCESSION NUMBER: 126:325794 CA
TITLE: Postnatal expression of **melanocortin**-3 receptor in rat diencephalon and mesencephalon
AUTHOR(S): Xia, Yun; Wikberg, J. E. S.
CORPORATE SOURCE: Dep. Pharmaceutical Biosci., Uppsala Univ., Uppsala, S-751 24, Swed.
SOURCE: Neuropharmacology (**1997**), 36(2), 217-224
CODEN: NEPHBW; ISSN: 0028-3908
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In situ hybridization was applied to examine the postnatal expression of **melanocortin**-3 (**MC**-3) receptor mRNA in the rat brain. Very weak and limited signals were seen in the hypothalamus on postnatal day 0 (P0) and in the dorsal lateral thalamus on P4. A marked increase was noted in several regions of the diencephalon and mesencephalon on P7. The highest levels were reached on P21, which was the time when an adult-like pattern was established. On P21, intense signals were seen in the ventromedial nucleus and the arcuate nucleus of the tuberal hypothalamus, the habenular nucleus of the epithalamus, and the ventral

tegmental area. [125I]Nle4,D-Phe7-.alpha.-MSH showed overlapping, but wider labeling of **melanocortin** receptors, that followed a similar developmental course. .alpha.-MSH-like immunoreactivity was seen widely in the forebrain and midbrain from P14. In contrast to the staining of .alpha.-MSH in neurons and their process, .gamma.2-MSH-like immunoreactivity was detected strongly in the blood vessels. The neuronal localization of **MC**-3 receptor mRNA suggests that this receptor may mediate the neurotropic actions of **melanocortin** peptides in the developing brain.

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(FILE 'HOME' ENTERED AT 14:31:56 ON 26 FEB 2002)

FILE 'CA' ENTERED AT 14:32:02 ON 26 FEB 2002

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L1          454 S SEX? DYSFUNC?
L2          862 S MELANOCORTIN?
L3           10 S MC-4R
L4            6 S MC-1R
L5           69 S MC4R
L6          117 S MC1R
L7           39 S MC3R OR MC-3R
L8        26945 S MC
L9           18 S MC5R OR MC-5R
L10          25 S MC2R OR MC-2R
L11         421 S MC!R
L12       27341 S L3 OR L4 OR L5 OR L6 OR L7 OR L8? OR L9 OR L10 OR L11
L13           5 S L12 AND L1
L14         282 S L12 AND L2
L15           5 S L13 AND L14
L16         277 S L14 NOT L15
L17          12 S L1 AND L2
L18           7 S L17 NOT L15
L19         277 S L16 NOT L17
L20         277 S L19 AND L2
L21          95 S L20 AND PY<1999
L22          17 S L21 AND (PHARM? OR DRUG?)
L23          78 S L21 NOT L22
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---Logging off of STN---

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Executing the logoff script...

=> LOG Y

STN INTERNATIONAL LOGOFF AT 14:44:12 ON 26 FEB 2002

Connection closed by remote host